SEP 11 1933
MEDICAL LIBRARY

ARCHIVES OF DISEASE IN CHILDHOOD.

EDITED BY

HUGH THURSFIELD, D.M., F.R.C.P., and REGINALD MILLER, M.D., F.R.C.P.

WITH THE HELP OF

H. C. CAMERON, M.D., F.R.C.P.
H. A. T. FAIRBANK, D.S.O., M.S., F.R.C.S.
LEONARD FINDLAY, D.SC., M.D.
A. DINGWALL FORDYCE, M.D., F.R.C.P.EDIN.
C. MAX PAGE, D.S.O., M.S., F.R.C.S.
LEONARD G. PARSONS, M.D., F.R.C.P.
G. F. STILL, M.D., F.R.C.P.
EDITOR OF THE *British Medical Journal*.

Vol. 8. AUGUST, 1933. No. 46.

CONTENTS

PAGE

Anæmia in Childhood.

Part VI. Nutritional anæmia in mother and child. By A. V. Neale, M.D., M.R.C.P., and J. C. Hawksley, M.D., M.R.C.P. 227

Part VII. Monocytic reaction in myelosis. By Robert Gittins, M.D., M.R.C.P., D.T.M. & H., and J. C. Hawksley, M.D., M.R.C.P. 241

Factors causing variation in the hæmoglobin level with age in the first year of life. By Helen M. M. Mackay, M.D., M.R.C.P. 251

Renal Rickets associated with parathyroid hyperplasia. By F. S. Langmead, M.D., F.R.C.P., and J. W. Orr, M.D., B.Sc. 265

On the occurrence of sex-linked variations in twins. By C. E. Kellett, M.D., M.R.C.P. 279

ISSUED BY THE BRITISH MEDICAL ASSOCIATION.

London: British Medical Association House,

Tavistock Square, W.C.1.

Yearly Subscription (6 numbers), 25/- *Single Number*, 4/6

GENERAL ADVISORY BOARD.

H. T. Ashby (Manchester).
W. R. Bristow (London).
Alan Brown (Toronto).
E. Cautley (London).
Glen Davison (Newcastle-on-Tyne).
T. Y. Finlay (Edinburgh).
G. B. Fleming (Glasgow).
Prof. John Fraser (Edinburgh).
Prof. W. E. Gallie (Toronto).
Sir Archibald Garrod, K.C.M.G. (Oxford).
J. F. Gaskell (Cambridge).
G. R. Girdlestone (Oxford).
H. Tyrrell Gray (London).
Robert Hutchison (London).
R. C. Jewesbury (London).
F. S. Langmead (London).
C. P. Lafage (Manchester).
W. L. Maccormac (Balham).
Helen Mayo (N. Adelaide).
T. P. McMurray (Liverpool).
Charles McNeil (Edinburgh).
A. E. Naish (Sheffield).
D. H. Paterson (London).
W. J. Pearson (London).
F. J. Poynton (London).
T. G. Pugh (Carshalton).
F. C. Pybus (Newcastle-on-Tyne).
Sir Humphry Rolleston, Bt. (Cambridge).
J. D. Rolleston (London).
J. C. Spence (Newcastle-on-Tyne).
E. H. M. Stephens (Sydney).
G. Bruton Swiet (Auckland, N.Z.).
C. W. Vining (Leeds).
E. H. Williams (Dunedin).

NOTICE TO SUBSCRIBERS.

Subscriptions are payable to the Financial Manager of the British Medical Association who has charge of all financial matters concerning the ARCHIVES OF DISEASE IN CHILDHOOD. Address: British Medical Association House, Tavistock Square, London, W.C. 1.

NOTICE TO CONTRIBUTORS.

All papers submitted for publication should be sent to Dr. Reginald Miller, 110, Harley Street, W. 1. All other editorial matters should be referred to Dr. Hugh Thursfield, 84, Wimpole Street, W. 1.

Papers sent for publication should be typewritten. Illustrations will usually be inserted in the text itself, and care should be taken that the text is marked to show the desired position of each illustration.

Charts and curves accompanying papers should be carefully drawn, on tracing linen. Any lettering on these drawings should be lightly inserted in pencil.

Contributors will receive one proof in page, but it is assumed that all but verbal corrections have been made in the original manuscript; an allowance at the rate of ten shillings per sheet of sixteen pages is made for alterations in the proof (printer's errors excepted), and contributors will be responsible for any excess.

Contributors will be supplied with reprints of their articles at cost price if application is made when returning proofs. An estimate of costs will be given if desired on application to the Financial Manager of the British Medical Association.

Papers which have been published become the property of the ARCHIVES and permission to republish must be obtained from the Editors.

STUDIES IN THE ANÆMIAS OF INFANCY AND EARLY CHILDHOOD

(From the Children's Hospital and the Department of Diseases of Children of the University, Birmingham).

Part VI.—Nutritional anæmia in mother and child

BY

A. V. NEALE, M.D., M.R.C.P.,

AND

J. C. HAWKSLEY, M.D., M.R.C.P.

The physiological relationships which exist between the mother and her child during pregnancy and lactation are intricate and complex. The normal material requirements for the adequate growth of the fœtus in utero are various, but under healthy conditions are remarkably constant and are met by placental transmissions. The fact that nature also demands that the mother shall transfer to the fœtus, particularly during the latter months of the pregnancy, certain materials to provide stores available for use during the early months of extra-uterine life, is a further example of the natural dependence of the infant upon its mother. On occasion these processes act adversely on the mother, and well recognized clinical disorders may be either produced or rendered apparent. The adverse effect of pregnancy in the osteomalacic mother is a clear though rare example of this, and it is now realized that examples in relationship to the blood are more common.

The disorders of the blood produced by pregnancy vary considerably in type and degree, simple hypochromic anæmia being of relatively common occurrence, whereas the more serious megalocytic anæmia of pregnancy fortunately is rare. In the hypochromic anæmia of pregnancy it is probable that transference of the maternal reserve of hæmopoietic substances to the fœtus is an important ætiological factor, and this is the more evident in the pregnant mother who through previous or present nutritional defect probably has poor reserves of iron, etc. Rapidly repeated pregnancies or multiple pregnancies are also contributory causes. Strauss and Castle[1] have shown that another important factor is the occurrence of gastric anacidity or hypoacidity. These writers also think that the megalocytic anæmia is due to a temporary lack of the specific intrinsic factor in the gastric juice, and that lack of the extrinsic factor from the diet may produce the same effect. Finally, they produce evidence to show that both varieties of anæmia may

exist in the same woman. Prescription of iron-containing foods or of medicinal iron, including copper, in adequate amounts during pregnancy will prevent the development of hypochromic anæmia; and an adequate diet, including yeast or marmite, and a potent preparation of liver, is therapeutically valuable in the megalocytic anæmia of pregnancy. It is, therefore, an important part of ante-natal supervision to enquire into the state of the maternal blood and to aim at the provision of essential hæmopoietic substances in adequate quantity in the dietary of the pregnant person. Several clinical workers have observed the ease with which maternal nutritional anæmia is produced in pregnancy; its prevention is usually also equally simple.

Anæmia in pregnancy may have far-reaching effects upon the fœtus in utero. Clinical observations which we have made show that nutritional anæmia may show itself in the new-born child, or become apparent during the milk-feeding period of early life. In our view there appears little doubt that a congenital anæmia may be a true nutritional anæmia, and that it may be due to deficiency in the maternal diet. The transference of hæmopoietic substances from the mother to the fœtus is progressive throughout pregnancy, and is considerably increased in the later weeks. This transference of iron and its allied hæmopoietic substances occurs in order to make provision for fœtal hæmopoiesis and to accumulate a store (principally in the liver) which will be available during the milk-feeding period of early life. It is recognized that such fœtal storage principally occurs in the latter weeks of the normal full-term pregnancy. It is, therefore, clear that if the total available quantity of iron, etc., in the maternal tissues is insufficient, there will be a deficiency of these substances in the developing fœtus, and a condition of simple anæmia may be expected to be present in the infant at or soon after birth. According to the majority of authorities infants born of anæmic mothers have normal blood pictures at birth: thus Baar and Stransky[2] state that anæmia of the mother does not produce anæmia in the new-born child, a statement with which Strauss and Castle agree.

We believe that this conception is erroneous, although an infant born of an anæmic mother is not necessarily anæmic. We base our belief partly on the evidence detailed in Part II of this series (p. 95) showing that nutritional anæmia can develop shortly after birth in rats whose mothers have been apparently cured of nutritional anæmia by yeast; and partly on the clinical evidence that we submit in the present paper.

The metabolic processes of calcium and iron are very similar, but there does appear to be one striking difference between them. The mother cannot retain calcium at the expense of the fœtus, but has to surrender it even if in doing so she contracts osteomalacia: whereas the mother can, and sometimes does, retain iron to the detriment of the fœtus. In the paper by Strauss and Castle to which reference has already been made, there is a chart

giving a graphic representation of the hæmoglobin percentages of the new-born infants of fourteen anæmic mothers. We have calculated out these hæmoglobin values and find that they range from 21·48 grm. per 100 c.cm. (154 per cent. Haldane scale) to 12·5 grm. per 100 c.cm. (91 per cent.) These results were obtained 'during the first few days after birth since there is normally a rapid decrease in hæmoglobin and erythrocytes in the first weeks of life.' Mackay[3] has recently pointed out that the normal hæmoglobin of the new-born child is about 140 per cent. on the Haldane scale (19·3 grm. per 100 c.c.). Using this standard there is evidence of at least one anæmic baby in the series of Strauss and Castle, despite their statement to the contrary. Moreover, there is definite evidence that in later infancy the children of anæmic mothers may show anæmia: thus in examining a series of pregnant women Mackay[3] found nine whose hæmoglobin was between 54 and 70 per cent., and the babies of these pregnancies showed a lower hæmoglobin level at every month for the first six months of life than the babies of non-anæmic mothers. Again, Strauss[4] found that infants who had not received treatment, and whose mothers were not anæmic during pregnancy, had an average hæmoglobin of 67 per cent.; whereas those whose mothers were definitely anæmic had an average hæmoglobin of 46 per cent.

The condition of the blood in these cases of simple nutritional anæmia of infancy is that of a hypochromic anæmia and has been fully described in a preceding paper (Part III, p. 117). Intercurrent infection may cause some change in the blood picture and immature forms of white cells may be seen on such occasions. Enlargement of lymphatic glands is absent, but the spleen may be palpable. The general nutrition of the baby may be otherwise good.

It is, therefore, a matter of interest to study cases of anæmia in the infant which are related to the maternal state, especially as treatment, both prophylactic and curative, is as a rule highly successful. In the present paper some of the examples which we have encountered are recorded and discussed.

In our series of cases nutritional anæmia has occurred in mother and/or infant (in some instances, in twins) in all possible combinations and permutations which can be represented as follows, where N stands for normal, and A for anæmic:—

	1	2	3	4	5
Mother	N	N	A	A	A
Infant	A	A	N	A	A
Twin	N	A	N	N	A

Examples of all these variations are recorded in the text.

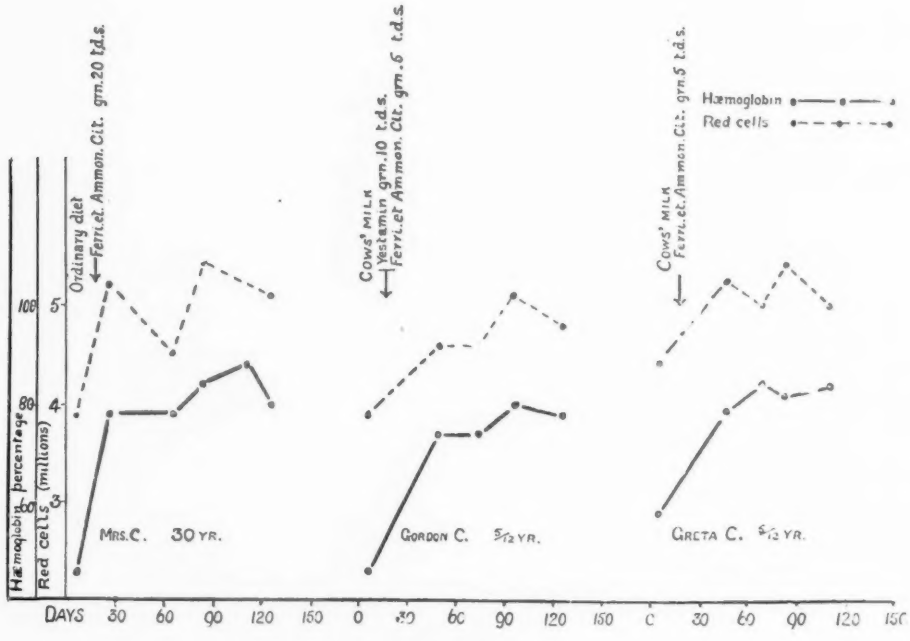
Anæmia in twin births.

Consideration will first be given to a number of instances of anæmia in twins: in some the mother was anæmic, and in others the mother was not anæmic.

Twins anæmic : mother anæmic.—We give first two examples of the twins of anæmic mothers showing anæmia.

Family 1 : (Chapman).—The mother had had three pregnancies in six years: (1) a girl; (2) twins, both male: one died, no known anæmia; (3) twins, male and female (the patients).

These infants came under observation in the first instance because the mother brought the male twin, Gordon, to hospital complaining that he was pale. The mother regarded herself as being in good health, although it was quite obvious that she had anæmia. The other twin, Greta, was considered to be healthy and was only brought to hospital on request.



Graph I.—Family 1.

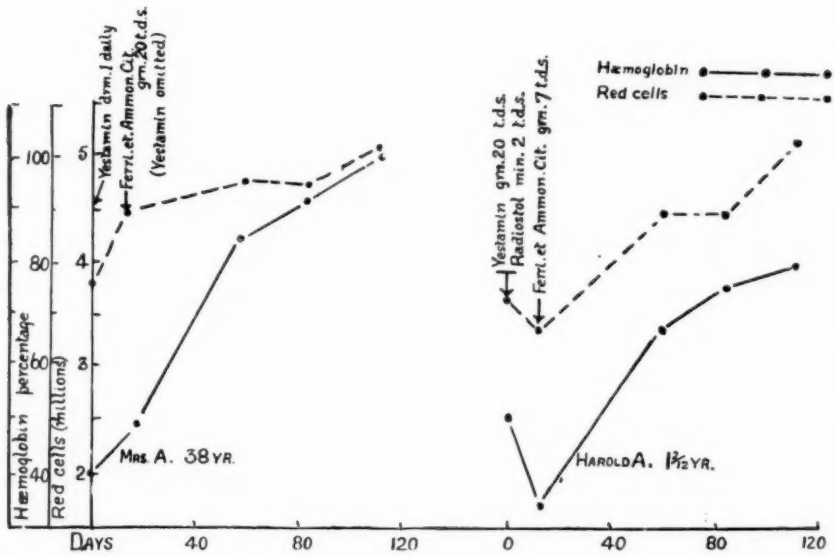
Mrs. C., aged 30. Never any serious disease. Had always taken a normal mixed diet. During and after the last pregnancy, however, she had not felt in good health and had at times considerable shortness of breath. Treatment by means of 20 grn. doses of iron and ammonium citrate, thrice daily, and ordinary diet resulted in cure.

Gordon C. Brought to hospital at the age of 5 months. Normal birth. Full term. Birth weight, 4 lb. Slight icterus neonatorum for a week, never hæmorrhage. Breast fed one month and then Grade A milk and rusks. When seen at hospital, good general nutrition; weight 14 lb.; very pale, no enlarged glands, no abnormal visceral signs, spleen not palpable, liver normal; no rickets,

Treatment consisted in giving 10 grn. doses of yestamin and 5 grn. doses of iron and ammonium citrate thrice daily. The child during that time was given cow's milk.

Greta C. (twin to Gordon). Birth weight 4 lb. Same history, previous to first hospital observation, and treatment given was similar except that in this case yestamin was not given.

The condition of the blood in the members of this family at the time they came under observation and the improvement under treatment is shown in Graph I. It will be seen that the mother and Greta were given iron, and Gordon (the more anæmic of the twins) was also ordered yestamin. In the course of twelve weeks all three became normal, and in excellent clinical condition. A recent observation found the children and mother in good health. The good nutritional state of the mother and twins apart from the anæmia was remarkable. The possible effect of recurrent twin



GRAPH II.—Family 2.

pregnancies as a factor in the hypochromic anæmia of the mother is suggested. The efficacy of the iron preparation, which contains copper, indicates that the cause of the anæmia was a simple deficiency of these essential substances. Probably the storage of iron in the maternal tissues before and during pregnancy was low, and a further depletion consequent upon the fœtal demands was sufficient to create the anæmia. The division between the twins, in utero, of what was probably a subnormal transplacental supply of iron is an adequate explanation of their hypochromic anæmia.

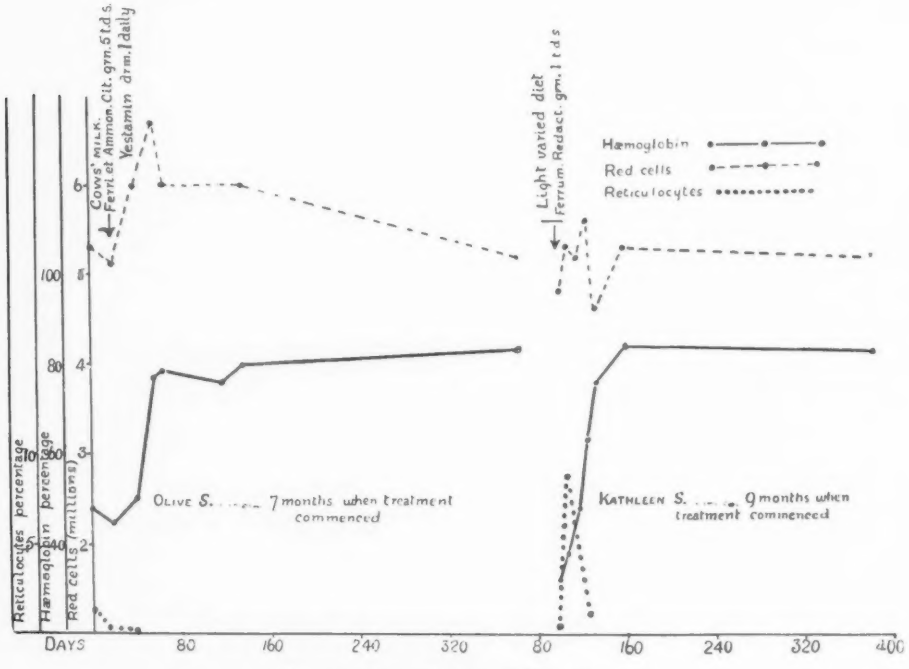
Family 2: (Allmark).—In this case also, the mother, although obviously anæmic, had sought no medical attention for herself, but brought her remaining twin to hospital because of his pallor and weakness.

Mrs. A., aged 38 years. Had six children in twelve years: four single pregnancies, and the last a twin pregnancy. During this last pregnancy she had been far from well with swollen legs, and was said to have nephritis of pregnancy. On a low diet all through the later months. Seen at hospital 12 months after the pregnancy and noticed to be pale, poorly nourished and weak. Urine showed a faint haze of albumin, but no cells or casts. Blood urea 42 mgrm. per cent. Wassermann reaction negative. The condition of her blood and the subsequent effects of iron and yeast therapy are shown in Graph II.

On December 17th, 1931, she was ordered 1 dr. of yestamin daily, but on January 1st, 20 grn. doses of iron and ammonium citrate, t.d.s., were substituted for this.

The twins. One died at the age of 10 months with diarrhœa. Both were pale, even as young babies. No icterus neonatorum. Full term pregnancy; normal labour.

Harold A. (surviving twin). Birth weight 4 lb. Fed on Cow and Gate milk, and later bread, butter, potato and gravy. At the first observation at hospital the infant weighed 13 lb.; pale and weak, constipation, no infection. No signs of visceral abnormality. No glandular nor splenic enlargement; no icterus; no rickets. Graph II shows the result of treatment.



Graph III.—Twins of Family 3.

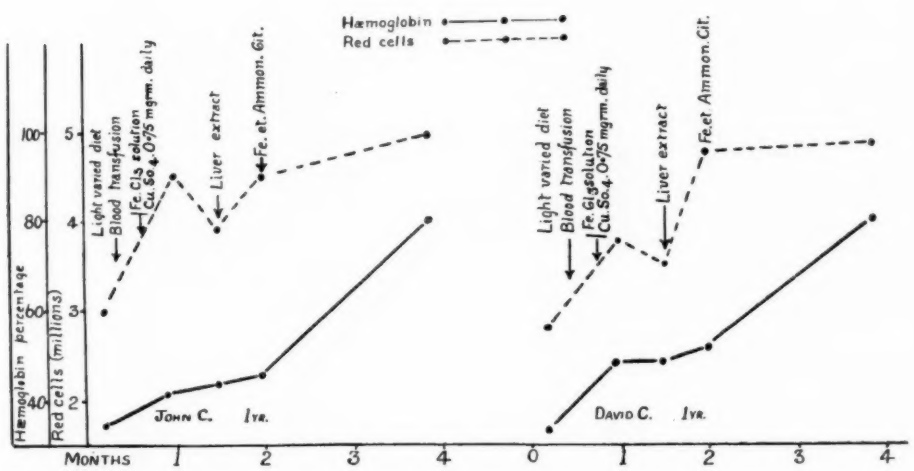
The clinical improvement (see Graph II) in mother and twin was marked, In this case there is a history of defective nutrition during pregnancy which was probably responsible for the development of maternal anæmia; further, true congenital anæmia appears to have been present in the twins. The mother and surviving child are now well.

Twins anæmic: mother normal.—The following cases are examples of anæmia in the twins and normal health in the mother; nevertheless, the nature of the anæmia is essentially the same as in the previous instances.

Family 3 : (Salmon).—Mrs. S. Healthy. Aged 27 years. Two previous single pregnancies and normal babies. Has had four children (including the present twins) in 8 years. During the twin pregnancy she had a little œdema of the legs. No anæmia. Full varied diet and always felt well and strong; when first seen at hospital 7 months after the pregnancy she was in excellent health and showed normal blood. Twins, normal labour.

Olive S. Full term. Birth weight 4 lb. Was very pale at birth and the mother says she didn't think it was strong enough to live. Never any hæmorrhage. No icterus neonatorum. Fed on Grade A cows' milk. Brought to hospital because of general weakness at the age of 6 months, and then weighed 11 lb. Observed to have considerable pallor without any visceral disease or glandular or splenic enlargement and no signs of any infective process. Graph III shows the blood condition, treatment and progress. Gained 10 lb. in weight during treatment.

Kathleen S. Birth weight 4½ lb. Same food as twin sister. This child was brought up for observation at our request at the age of 11 months and found to be extremely pale. Weight 19 lb. 1 oz. No glandular nor visceral enlargement. Had been pale since a ' very small baby ' and become progressively whiter. There had been no icterus at any time. Occasional simple diarrhœa. No evidence of any infection. Weight increased 7 lb. during treatment by reduced iron.



GRAPH IV.—Twins of Family 4.

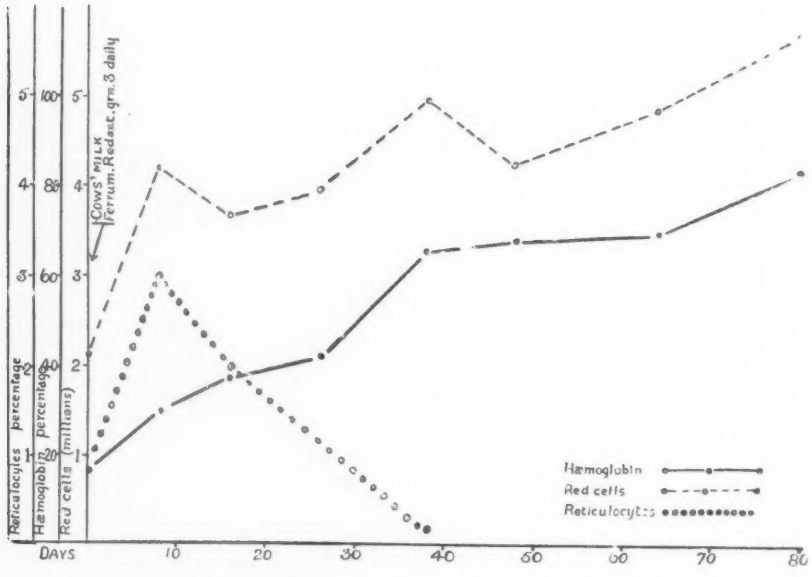
As indicated in Graph III each child showed rapid improvement, and it is interesting to observe that although each twin at the commencement of treatment had a good count of red corpuscles the hæmoglobin level was low. The rapidity of the increase in hæmoglobin production in Kathleen S. on reduced iron was remarkable, there being a rise from 30 to nearly 80 per cent. in about six weeks, with corresponding improvement in her general condition. It is clear that the cause of anæmia in these twins was an intra-uterine deficiency in iron and possibly other hæmopoietic substances. In the previous single pregnancies none of the children had shown any infantile anæmia. The twins are now in excellent health.

Family 4 : (Chamberlain).—In this family the parents both came to hospital and were obviously in perfect health, whereas each twin was remarkably pale.

Mrs. C., aged 28 years. Always in first class health; excellent colour. Blood normal. Living on full varied diet. This twin pregnancy was her first. The twins were born at 8 months; labour normal.

Twins: John C., 1st born. Birth weight 4 lb. David C., 2nd born. Birth weight $3\frac{1}{4}$ lb.

Both babies pale at birth but no icterus observed. At 3 months their pallor was recognized by the parents and became more marked, although no medical attention had been sought. Both boys were brought to the hospital for the first time at the age of 12 months, obviously suffering from anæmia with weakness, shortness of breath and anæmic anoxæmia. Their general nutrition, however, was not bad since John had reached 16 lb. and David 14 lb. 14 oz. The boys were so seriously ill that immediate admission to the hospital was advised. There were no hæmorrhages nor purpura, and the retinæ were clear. Each had been breast fed for one month, and then changed to a dried milk with occasionally rusks, custard and beef tea. Soon after admission each child was given a blood transfusion.

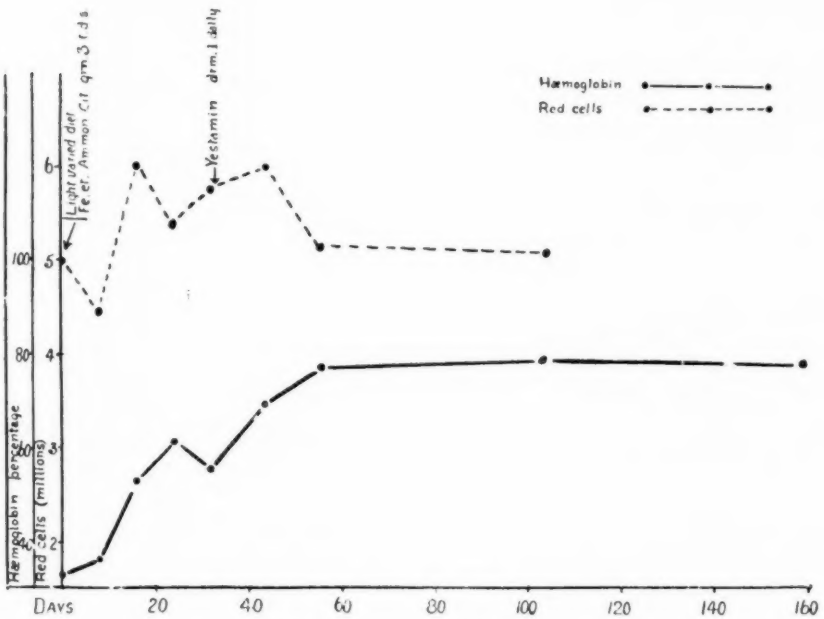


GRAPH V.—Anæmic twin in Family 5.

The condition of the blood is shown in Graph IV and a record of the progress in hospital and medicinal therapy is indicated. This was one of the earliest cases of the series in which the direct use of iron and copper salts was made. A weak solution of ferric chloride in milk was given, together with 0·75 mgrm. of copper sulphate. The use of these substances tended to cause diarrhœal disturbance, but the red blood cells and hæmoglobin increased. Liver extract was utilized at one point and appeared to have acted as an added stimulus to erythrogenesis. The exhibition of iron and ammonium citrate, however, caused a rapidly progressive

increase of hæmoglobin and finally, after a total period of about 16 weeks, the blood had assumed a nearly normal level. Each boy has been examined again recently, and their health is perfect. John weighs 35 lb. and David 34 lb. (aged $2\frac{1}{2}$ years).

The ætiological importance of prematurity and twinning in the rapid development of hypochromic anæmia is exemplified by these infants. The lack of full-term development and even more important the failure to receive the specially abundant supply of iron, etc., which occurs in the ninth month of gestation, appear to have caused the rapid development of anæmia. Physical growth after birth was not materially delayed; in fact the progressive increase in weight doubtless accentuated the effects of the anæmia. It is not known if these were identical twins, or what the placental arrangement was.



Graph VI.—Anæmic twin in Family 6.

One twin anæmic ; other twin normal ; mother normal.—The following two cases are instances of anæmia occurring in only one of a pair of twins.

Family 5 : (Bate).—Mrs. B., aged 25 years. First pregnancy single child 18 months before the birth of twins. Always in excellent health and never anæmic. Quite normal during twin pregnancy and lived on a full diet. Twins: normal labour; full term; both boys.

Malcolm: Birth weight 6 lb. 8 oz. Excellent colour at birth and has remained perfectly healthy. Blood normal on examination.

Peter: Birth weight 5 lb. 2 oz. Pale at birth. No icterus. Brought to hospital at the age of 4 months because of marked pallor and weakness. No enlarged spleen nor lymph glands. Each twin was fed in exactly similar manner on cows' milk.

The progress under treatment of the anæmic twin is shown in Graph V.

The remarkably low hæmoglobin value and red blood cell count on initial observation is in extreme contrast with the normality of the other twin's blood. The same milk diet was continued in hospital and ferrum redactum, grn. 3, daily, was added. The response was rapid and progressive and in about 12 weeks the blood was normal. The boy now weighs 22 lb., but has not quite reached the weight of his normal twin brother Malcolm.

There is practically no doubt that this was a case of nutritional anæmia in the new born. An unequal distribution of hæmopoietic substances to the developing twins in utero is evident. The anæmic twin was also 1½ lb. smaller at birth. In this case there was gross defect in the number of red blood cells combined with an extremely low hæmoglobin.

Family 6 : (Hewitt).—Mrs. H., aged 38 years. Two pregnancies in 16 years. Always good health, never anæmic; normal pregnancy; blood normal.

Denis: Birth weight 6 lb. 6 oz. Always in excellent health; normal birth; full term; blood normal.

Doris: Birth weight 5 lb. 1 oz., breast fed. At three months pallor evident. When seen at hospital, aged 10 months, very pale, weak, and irritable. No enlarged glands; spleen just palpable. No infection. Never any icterus. Blood count showed an adequate number of red blood cells but the hæmoglobin was only 34 per cent. Treatment effected a rapid improvement and after 14 weeks the hæmoglobin had risen to 82 per cent. Graph VI illustrates the clinical course. At the age of 20 months she weighed 28 lb. and was in perfect health.

This is a typical case of severe hypochromic infantile anæmia in one twin, the other being from birth onwards free from any blood abnormality. The anæmia was due to defective hæmoglobin formation consequent upon low iron storage at birth. Again the latter phenomenon was evident in the smaller twin. Since the pregnancy was carried to the full term no cause can be adduced other than an inadequate transfer, or the possibility of markedly unequal distribution, of iron to the fœtuses from the healthy mother.

Anæmia in single births.

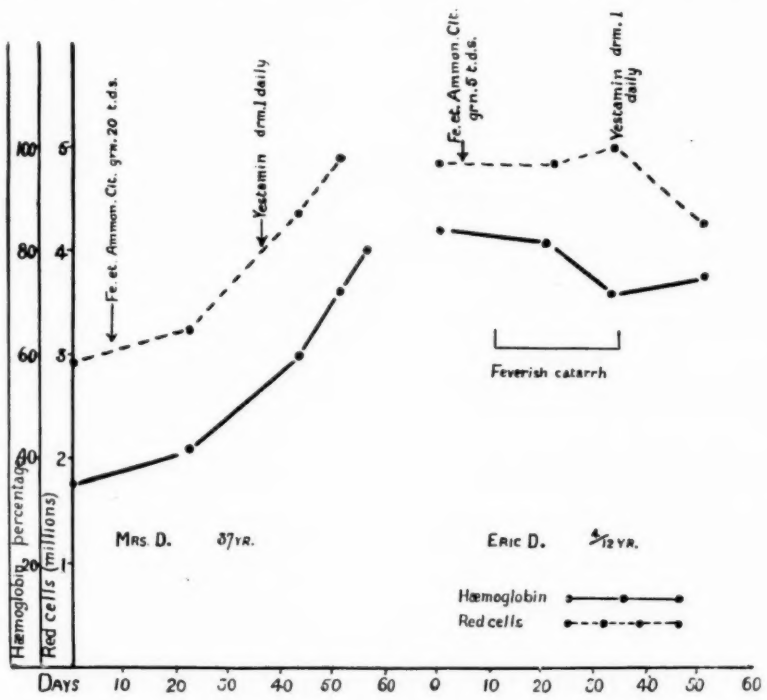
Infant normal ; mother anæmic.—The picture presented when a severely anæmic mother is seen carrying her healthy good-coloured baby is an arresting one and immediately arouses the suspicion that nature has attempted to leave the infant in good condition at birth irrespective of maternal health. Such a process holds with remarkable constancy in healthy babies born of tuberculous mothers, true congenital tuberculosis being an extremely rare occurrence. In the following cases a healthy baby was born of a severely anæmic mother.

Family 7 : (Davis).—Mrs. D., aged 37 years. Said to be always pale and when first seen at hospital she was pale and weak but of moderate general nutrition. She had developed more marked pallor during the pregnancy which otherwise had been normal. No renal disorder nor any evidence of systemic disease. No splenic nor glandular enlargement and no signs of infection. No hæmorrhages. Examination of the blood revealed less than 3,000,000 red blood cells per c.mm. and hæmoglobin 35 per cent., giving a colour index of 0·6. Microscopically the red cells showed no marked aberration, were normal in size and no immature forms were present. Leucocytes normal. Advice was given about her diet and iron and ammonium citrate, 1 drm. daily, prescribed, with the result that there was a moderate rise in red

cells and hæmoglobin. Three weeks later yestamin was also added and a marked acceleration of the hæmopoietic activity occurred so that at the end of a further period of four weeks an improvement was clinically obvious. One month later again the cure was definite and the mother said she had never had such a good colour nor felt so well.

Eric D., born a month prematurely, $5\frac{1}{4}$ lb. at birth. He was a normal colour and has remained so, in sharp contrast with the mother's pallor. First seen at hospital at 4 months when he had reached 9 lb. in weight and appeared physically well. Feeds had consisted entirely of Grade A milk. The blood count showed 4,900,000 red cells per c.mm. and 85 per cent. hæmoglobin. Leucocytes and platelets normal.

The result of the blood examination of mother and baby are shown in Graph Vll. The fall in the baby's hæmoglobin after the 30th day was due to coryza and bronchitis.

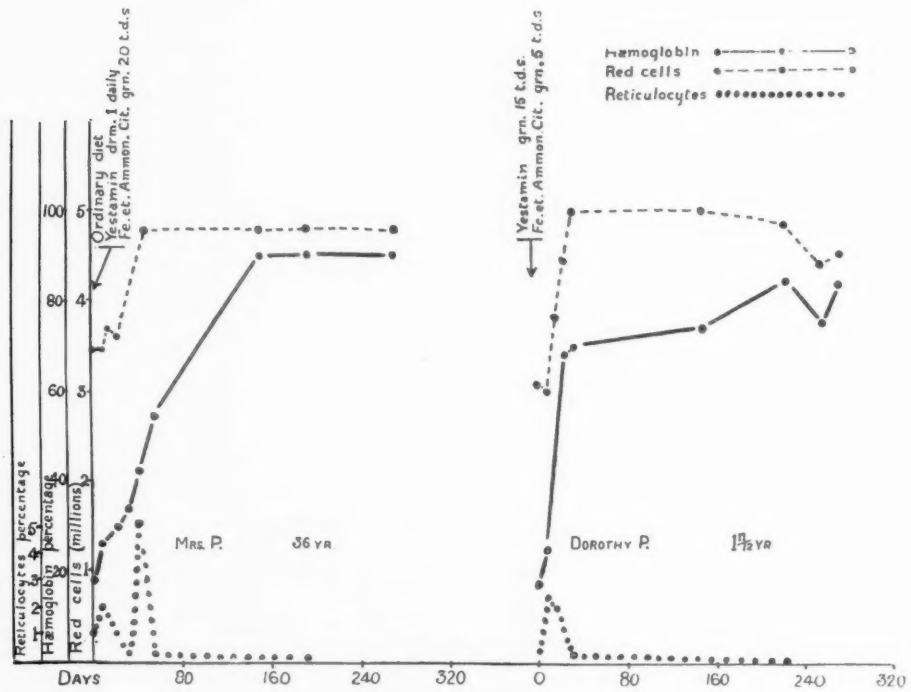

Fe. et Ammon. Cit. grn. 20 t.d.s.
Yestamin drm.1 daily
Fe. et. Ammon. Cit. grn. 5 t.d.s.
Yestamin drm. 1 daily
Feverish catarrh
Hæmoglobin percentage
Red cells (millions)
Mrs. D. 37 yr.
Eric D. 5/12 yr.
Hæmoglobin
Red cells
Days 10 20 30 40 50 60 0 10 20 30 40 50 60

Graph VII.—Mother and baby in Family 7.

This case shows the interesting phenomenon of normal hæmopoiesis in a baby born of a mother suffering from hypochromic anæmia preceding and during pregnancy. The adequate transfer here of hæmopoietic substances in utero, is even more remarkable when it is understood that the baby was four weeks premature. This is, perhaps, the most striking case which we have seen as a clinical example of adequate transplacental nutrition and fœtal storage of essential blood-forming substances at the expense of the mother: the latter being sufficient to increase the maternal anæmia during the pregnancy. The simple nutritional cause of the hypochromic anæmia is indicated by the rapid cure which followed an adequate supply of iron preparation. Yeast acted as an extra stimulant and illustrates the advantage which is sometimes seen when the two substances are prescribed together.

Infant anæmic: mother anæmic.—The following is a very good example of anæmia in mother and child.

Family 8: (Prately).—Mrs. P., aged 36 years. Gave a history of pallor since aged 12 years, worse during past few years. Had always taken an ordinary diet, but rarely any meat foods. She had borne four children in 6 years, the present patient being the fourth. The first baby died of anæmia, the second and third were healthy. She had no hæmorrhage. Menstruation normal. No dyspepsia. Had always been an average weight. She came under hospital observation when she brought the baby Dorothy, aged 1 year 11 months, for treatment, and appeared extremely pale and of poor physique. She had not sought any advice for herself and was surprised when it was suggested that she should also become a patient. A blood examination revealed red blood cells 3,500,000 per c.mm. and only 18 per cent. hæmoglobin; colour



GRAPH VIII.—Mother and baby in Family 8.

index 0·25. The red cells were normal in size and no immature forms were present. There were no glandular enlargements, splenic nor hepatic abnormality, and no icterus. No signs of any infective process. When first seen was ordered 1 drm. of yeast daily and 20 grn. of iron and ammonium citrate, twice daily.

Dorothy P., normal birth, full term. Birth weight 3 lb. Only weighed 5½ lb. at eight weeks. Fed on Ostermilk and cow's milk, and later bread, butter, potato and occasional gravy. She had been pale since birth. On first examination at the age of 23 months she was extremely pale and asthenic; no glandular nor splenic enlargement, and no evidence of avitaminosis; no purpura, nor hæmorrhage. Blood Wassermann reaction of mother and child negative. The blood, as in the case of the mother, showed only 18 per cent. hæmoglobin and red blood cells 3,080,000; colour index 0·25. Microscopically the erythrocytes were free from any abnormal features

regarding size, shape or nucleation, and only 0·3 per cent. reticulocytes were present. When first seen she was ordered 15 grn. of yeast daily, and 5 grn. of iron and ammonium citrate, thrice daily.

It is therefore evident that both mother and child were suffering from a severe grade of simple hypochromic anæmia, clearly of nutritional origin in the mother. In the child the anæmia was related to congenital malnutrition, and intensified by inadequate feeding during the latter year of her existence. Medicinal treatment was immediately given, the child being admitted for this purpose and the mother attending regularly in the out-patient department. Graph VIII illustrates the progress in each instance.

The therapeutic response is specially noteworthy. During the first four weeks the baby increased her red cells from 3,080,000 to 5,010,000, and hæmoglobin 18 to 70 per cent. Mrs. P. showed similar but less rapid hæmopoiesis and a reticulocytosis to 5 per cent. After 12 weeks treatment with an iron preparation and dried yeast the patient appeared clinically cured, and soon afterwards the respective blood counts were quite normal. There was coincidentally an increase in the baby's weight of 5 lb. in about 12 weeks and a corresponding improvement in general health. Both are now (one year after first attending hospital) in perfect health.

The intense degree which simple hypochromic anæmia of nutritional origin may reach is demonstrated in this family. The prolonged anæmia in the mother was considerably intensified during the pregnancy owing, doubtless, to the further withdrawal of maternal hæmopoietic substances by the fœtus. Few infants have entered life in a more pathetic state of health, weighing only 3 lb. (at full term), and being very ill supplied with the requisite substances for its blood formation, an effect continued by the poor dietary until attendance at hospital. The ultimate result, however, shows how well even the advanced case will respond to iron medication.

Conclusion.

The biological problems discussed in this paper once more emphasize the value of adequate infantile storage of iron, etc., at birth and the importance of a mixed dietary at least after the first nine months of life. The experiments of C. M. Davies[6], which showed the natural inclination for babies, at about the age of nine months, to help themselves with a varied diet when such was provided, are important indications of the necessity for such a diet.

There seems no doubt that the foregoing cases are in themselves sufficient demonstration of the efficacy of the therapeutic agents employed. A great deal of experimental work has been carried out recently in the attempt to show the possible mechanisms of production and cure of the types of hypochromic anæmia seen in infants. Reference has been made in preceding papers in this series to the results of this work, but it may be recalled that we have shown that the addition of yeast to the milk diet of rats suffering from nutritional anæmia will cure the anæmia and allow reproduction to occur. The members of the resulting litter, however, showed nutritional anæmia. The addition of yeast and pure iron in adequate quantities to a milk diet not only ensures the cure of nutritional anæmia in anæmic rats, but also that the members of any litter they produce then have a hæmoglobin above normal. The clinical cases recorded in this paper furnish direct human corroboration of these and other experimental studies,

REFERENCES.

1. Strauss, M. B., & Castle, W. B., *Amer. J. Med. Sci.*, Philad., 1933, CLXXXV, 539.
2. Baar, H., & Stransky, F., *Die Klinische Hematologie des Kindersalters*, Leipsic, 1928.
3. Mackay, H. M. M., *Med. Res. Council*, London, 1931, Sp. Rep., No. 157.
4. Strauss, M. B., *J. Clin. Invest.*, Baltimore, 1933, XII, 375.
5. Mackay, H. M. M., *Arch. Dis. Childh.*, London, 1933, VIII,
6. Davies, C. M., *Am. J. Dis. Child.*, Chicago, 1928, XXXVI, 651.

Part VII.—Monocytic reaction in myelosis

BY

ROBERT GITTINS, M.D., M.R.C.P., D.T.M. & H.

AND

J. C. HAWKSLEY, M.D., M.R.C.P.

We have recently recorded[1] a case of monocytic leukæmia in a child in which autopsy and histological examination revealed a generalized reticulo-endotheliomatosis.

The case here recorded is one in which the blood picture for a period of nearly six months showed a leucocytosis with marked increase in the number of circulating monocytes, and together with the clinical findings made monocytic leukæmia the most probable diagnosis. Unfortunately for the four months immediately preceding her death the child was not seen. A post-mortem examination obtained by the help of Dr. Dingley and Dr. Morris, of Wednesbury, revealed no evidence of the previous monocytosis, and showed that death had been due to myelogenous leukæmia.

Case report.

I. C., female, was born in October, 1930. She was the fifth child, three of the others being alive and one having died of gastro-enteritis. Born at term, she weighed 8 lb. She was never breast fed, and was reared on Cow and Gate food. At the age of 10 months, when the weight was 17 lb., her mother observed that the child's abdomen was enlarging. She was observed to have bruising of the arms and legs and face and subconjunctival hæmorrhages; her tonsils were enlarged and she was anæmic. The liver and spleen were enlarged. No other abnormal physical signs were noted. She improved considerably with general treatment, but 2 months later, at the age of 12 months, she began to show a rise of temperature and was admitted to the Birmingham Children's Hospital.

On admission the child looked ill and slightly anæmic. She was of average build and weight, and had no elevation of temperature. There was no jaundice. The heart and lungs showed no abnormality. Her liver was enlarged and smooth, and her spleen greatly enlarged, extending down to the left anterior superior spine, and quite smooth. The glands of the neck, axillæ and groins were all slightly enlarged, discrete and not adherent to surrounding tissues. There was no rickets. Beyond a few small and fading ecchymoses on the legs, there were no signs of purpura. The mother's Wassermann reaction was negative, and the child showed a negative Mantoux reaction.

The condition of her blood on admission is shown in the table. Bleeding time, clotting time and fragility of the red cells were normal.

A week after admission the child developed a transient gastro-enteritis with marked dehydration. At the same time her spleen was much reduced in size, and in the peripheral blood an increase in the number of white cells was noted. This latter phenomenon was interpreted as being due, at any rate in part, to the outpouring of cells from storage in the spleen in response to its contraction. She recovered from this attack and her blood picture, apart from the leucocytes, improved and remained fairly steady. The spleen increased again in size, though not to its former extent.

She was kept in hospital for 4 months, during which time 14 blood examinations were made; 7 of these at approximately monthly intervals are set forth in the table. Her weight chart showed a steady gain, her colour, temper and appearance soon became those of a healthy infant; but the white cell count remained raised, and the monocytes ranged always from about 20 to 40 per cent. of the leucocytes. The spleen, while varying from week to week, was always much enlarged, and the liver remained enlarged throughout. X-ray examination of her bones revealed no abnormality. Apart from one ecchymosis on the forehead, no signs of purpura were observed.

The diagnosis was regarded as probably one of monocytic leukæmia, but as her condition was so good after 4 months in hospital she was allowed to go home.

She attended the out-patient department for two months and for this period continued to be in good condition. Her last blood count, two months after leaving hospital, showed a fall in the hæmoglobin and red cells, and re-admission was suggested. Unfortunately the parents transferred the child to the care of a welfare centre, and she was not seen again alive by us. She died four months later.

Date.	26.10.31.	31.10.31.	27.11.31.	30.12.31.	23.1.32.	2.3.32.	13.4.32.
Red cells	5,490,000	5,960,000	5,596,000	5,231,000	4,453,000	5,142,000	3,853,000
Hæmoglobin, p.c. ...	66	68	56	56		70	58
Colour index	·6	·57	·5	·54		·69	·75
Leucocytes	32,500	81,000	32,400	24,500	20,000	16,500	15,900
Platelets	320,000	84,000	49,000	164,000	71,000	53,000	
Neut. polymorph. ...	23·5	25·5	33·0	26·5	23·5	21·0	25·0
,, myeloblasts ...	1·0	0·5					
,, myelocytes ...	4·5	1·0					1·5
,, metamyelocytes	9·5	2·0	3·5	2·0	3·5	3·0	3
Eosinophils	2·5	0·5	3·0	1·5	2·0	3·5	1
Basophils	0·5		3·0	1·0	0·5	1·0	2
Monocytes	29·5	43·0	26·5	36·0	18·5	25·0	35·0
Lymphocytes	29·0	27·5	31·0	32·5	51·5	46·0	32·5
Türck cells				0·5	0·5		
Normoblasts	1·0					0·5	1·0
Megaloblasts		0·5					
Polychromasia	+	trace	+	+	+	+	
Anisocytosis	+	trace	+	+	+	+	
Poikilocytosis	+						
Reticulated corpuscles	2·8	0·6	0·4	1·2	1·0	0·8	

Reference to the Table will show that for nearly 6 months (October, 1931, to April, 1932), the white cell count was raised to between 15,900 and 81,000 per c.mm. The erythrocyte counts were normal until the last few blood examinations, in which a tendency to fall is noted, particularly in the last count of April 13th, 1932. The hæmoglobin during the period under observation varied between 52 and 70 per cent. In other words, beyond showing a slight hypochromic anæmia at times, the erythron was not affected except at the time of the last count. The reticulocyte counts indicated a normal, or at times slightly over-active, red-cell marrow. Except in the first count, the platelets were always below normal in number.

Apart from the constant and varying degree of leucocytosis, two points stand out in the differential distribution of the white cells; first, the high percentage of typical monocytes; and secondly the tendency towards immaturity of the myeloid cells, as shown by the constant appearance of young forms in numbers slightly greater than normal. The lobulation of the mature polymorphonuclear cells was also suggestive of immaturity, and it was unusual to find more than one or two cells with more than two lobes,

The appearance of the various white cells was carefully watched. Immature lymphocytic cells were not seen. The immature myeloid cells were quite typical. The monocytes were of mature type and presented in themselves no abnormality; the nuclei were oval or kidney-shaped, the nucleoplasm staining in the typical streaky way with Leishman's stain. The cytoplasm was of the bluish opalescent type, some of the cells having fine pink cytoplasmic granules. Pseudopodia were not present, and there was no resemblance to the histiocyte. The oxydase reaction was negative.

On first seeing the child the diagnosis on clinical grounds of von Jaksch's anæmia suggested itself. The blood examinations, when added to the clinical findings, indicated two possibilities, infective mononucleosis or monocytic leukæmia. After following the case, however, for six months with little if any change for the worse on the one hand or improvement on the other, the tendency was to distrust either diagnosis.

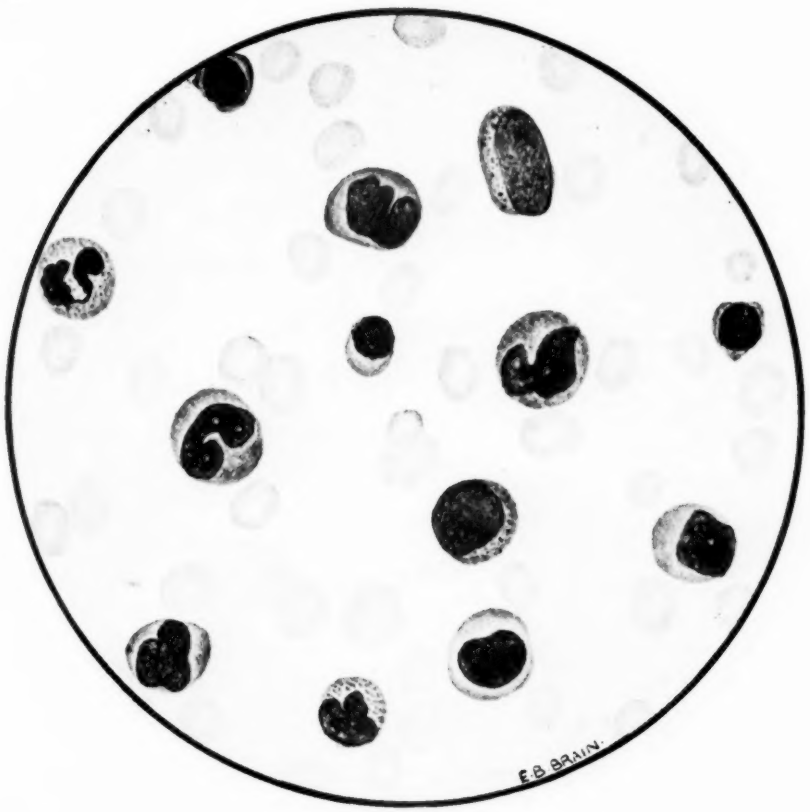


FIG. 1.

Composite drawing of monocytes; mature lymphocytes are also shewn.

What occurred in the blood between her last examination and her death must remain a mystery, but the histological examination of the tissues throws some light on this problem.

Autopsy.—Body of a moderately nourished pale child showing many scattered fine petechiæ.

THORAX.—Thymus was slightly large. Lungs showed terminal broncho-pneumonia, especially in the lower lobes. Mediastinal glands were grossly and uniformly enlarged, rather red-pink in colour. Pericardium showed a few petechiæ, and contained a few drachms of straw colour fluid. Heart was pale, flabby, and showed a few petechial hæmorrhages.

ABDOMEN.—Peritoneal cavity contained a small quantity of free fluid. The liver was considerably and uniformly enlarged, and showed on section a fine thickening of the portal tracts, rather similar to an early interlobular cirrhosis; no deposits; some fatty degeneration. The spleen was grossly enlarged and extended almost to the pelvic brim; no deposits, surface smooth. The kidneys were pale. The mesenteric glands were moderately enlarged, fairly soft and pink. In the inguinal and lumbar regions were scattered moderately enlarged lymph glands. No abnormality was noted in the other organs.

PHARYNX.—Both tonsils were much enlarged and presented a somewhat fungating, red smooth and lobulated surface towards the midline.

BONE MARROW.—In the femur (shaft) the bone marrow was copious, pink and cellular.

Histological examination.—Tissues were placed in formalin approximately 36 hours p.m. (August), and sections were stained with hæmatoxylin and eosin.

BONE MARROW.—The low power showed the marrow to be unusually cellular, though red cells were extremely scanty; the white cells were of various shapes with round forms prepondering. Under the high power a large number of myeloblasts were found: these cells had round or slightly oval nuclei, with well defined nuclear membrane and one or more nucleoli; their average size was 8μ. Myelocytes and metamyelocytes with kidney-shaped nuclei were numerous. Though their nuclear shape was similar to that of monocytes, they were smaller; their structure was of the same nature as the other cells of the granular series. Very few mature polymorphonuclear cells were to be seen. Eosinophil cells, immature and mature, were numerous. A fair number of small darkly staining round cells were scattered amongst the myeloblasts. These showed scarcely any cytoplasm. The nuclei stained more deeply than those of the lymphocytes in the lymph glands. It is probable that these dark cells were normoblasts, the cytoplasm of which had been lysed on account of the delay of 36 hours before autopsy. Reticular cells were to be made out in small numbers; they appeared normal. In brief the marrow represented an advanced myelosis. There was marked immaturity of the myeloid series, but erythropoiesis was present.

LIVER.—There was a moderate infiltration of the portal tracts with small round cells with a few myeloid cells which shewed the appearance of myeloblasts. Though the sections were taken 36 hours after death, the cells stained well and there was little degeneration of the central hepatic cells: myeloblasts, myelocytes, metamyelocytes and polymorphonuclear cells were found in the sinusoids. No areas of metaplasia were seen. Mitoses were not found. The Küpffer cells were normal.

LYMPH GLANDS.—Under the low power the lymph follicles were somewhat difficult to make out owing to the large number of white cells in the pulp. There was some congestion of the blood vessels, which shewed a greatly increased proportion of white cells in their lumina. In the pulp were scattered small clumps of larger, round and more deeply staining cells, which under higher magnification proved to be myeloblasts. Under the high power the centres of the lymph follicles and the pulp shewed slight increase in reticular fibres. Myeloblasts were found mingled with lymphocytes on the outskirts of the lymph follicles. The lymph sinuses contained many myeloblasts. Throughout the pulp was a good proportion of lymphocytes with plentiful small clumps of myeloblasts and practically no red cells. The monocytes, present in the high proportion of 30 per cent. in the peripheral blood 4 months before death, did not appear to be present, since but few large lightly staining cells were to be found. Reticular cells were distinguishable, and apart from slight increase in number and in amount of fibrous processes, were normal in appearance. Fine granules of brownish pigment of hæmatoidin were scattered in the reticular network.

SPLEEN.—As in the lymph glands, the lymph cords were relatively indistinct owing to the cellularity of the pulp. Fibrous tissue was slightly increased. The endothelial

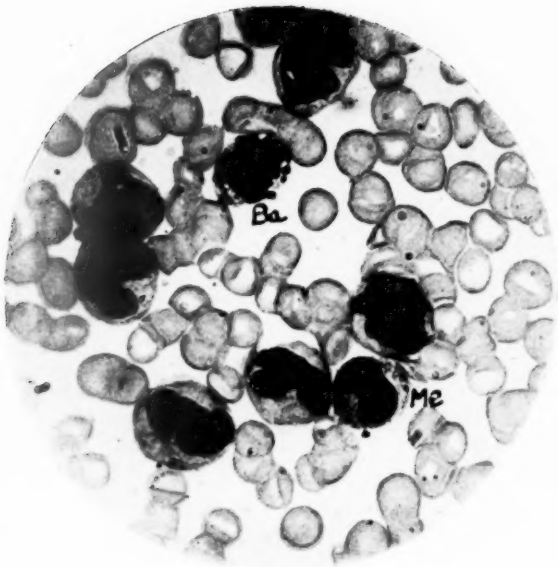


FIG. 2.

Microphotograph of monocytes. An immature metamyelocyte (Me) and basophil (Ba) are also shewn (x 820: Leishman).

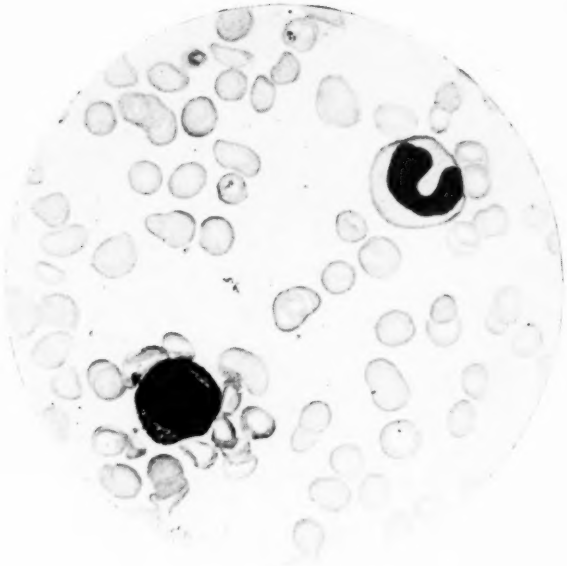


FIG. 3.

Microphotograph of monocyte and a myelocyte (x 725: Leishman).

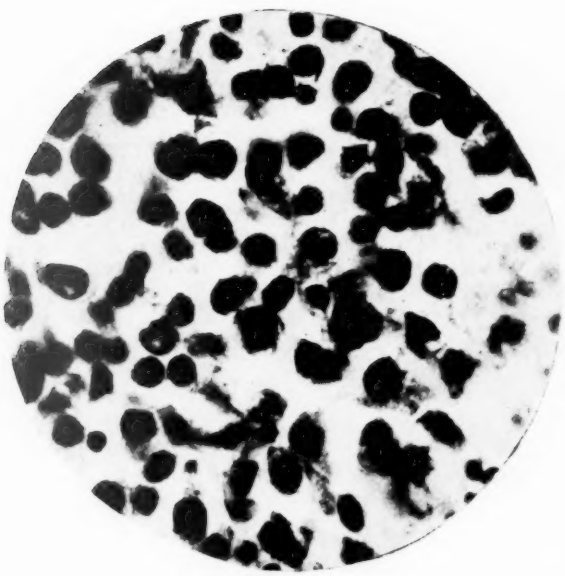


FIG. 4.

Microphotograph of marrow, showing myeloblasts and some normoblast nuclei (x 725: H.E.)

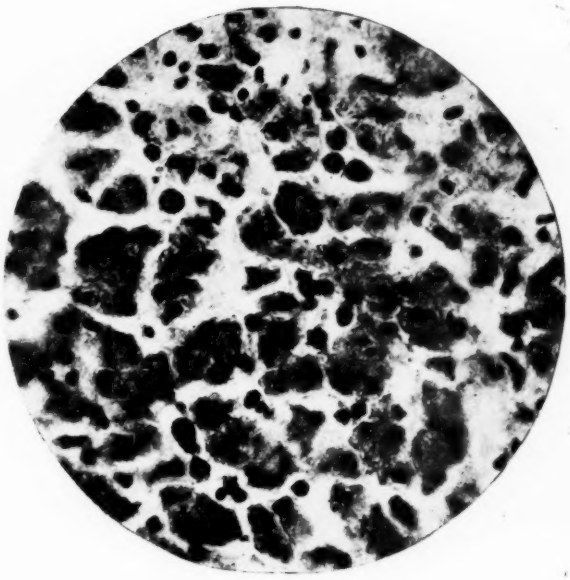


FIG. 5.

Microphotograph of liver, showing myeloid cells in sinusoids; Küpffer cells normal or somewhat smaller (x 400: overstained H.E.)

tissue in the centres of the lymph follicles was slightly proliferated and amongst them a few cells of monocyte type were seen. The cytoplasmic processes of these were not visible probably owing to post-mortem change, but the nuclei were about 9μ in the longest diameter, and of kidney shape; the size of these cells was therefore considerably greater than that of the myeloblasts.

The most striking cells in the pulp were myeloblasts which were aggregated here and there into small clumps of half a dozen or more, and most were approximately 8 to 10μ in diameter. More mature cells of the granular series were fairly numerous. Here and there a very few more lightly staining cells with kidney-shaped nuclei were to be made out; these were possibly monocytes, but their number was extremely small. A number of eosinophil cells, generally younger than polymorphonuclears, was present.

There was a general increase in the fibres and cells of the reticulum; a few of the nuclei of the reticulo-endothelial cells were somewhat swollen, and their processes blunter and stouter. The increase in reticular fibres tended to vary in amount.

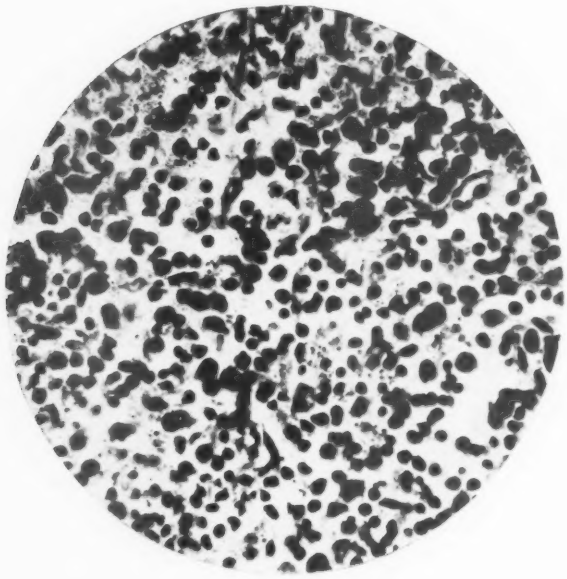


FIG. 6.

Microphotograph of spleen, showing small clumps of myeloblasts in lymph follicle. The dark dots appeared to be nuclear fragments (x 525 : H.E.)

Another section examined showed in one area cellular proliferation of the endothelium with myeloblasts present in it. Some of these myeloblasts appeared to have blunt processes and to be only partially free. In other respects they were similar to the free myeloblasts. It thus appeared that there was some myeloid metaplasia in the pulp of the spleen. Red cells were almost absent. No giant cells were found.

KIDNEY.—The glomeruli appeared more cellular than normal, but myeloblasts were not detected in their capillaries. Capsules were normal. The convoluted and spiral tubule cells were pigmented and cloudy in appearance, and the nuclei stained faintly; these changes were in large part due to post-mortem autolysis. Most of the cytoplasm of the other tubules was missing, so that nuclei appeared numerous, No leukæmic infiltration was discovered,

LUNG.—There were marked bronchial catarrh and desquamation of epithelium. Areas of collapse and compensatory emphysema were numerous. There were also areas of pneumonia where the alveoli contained many macrophages, laden with greenish-gold pigment, desquamated epithelial cells and young neutrophil leucocytes. The arterioles contained many similar neutrophils and some myeloblasts, and surrounding the vessels were small leukæmic infiltrations of myeloblasts. A few somewhat larger areas were composed entirely of round myeloblasts, packed so densely, that it appeared that myeloid metaplasia was present. Search, however, failed to reveal mitoses. A similar area was found in the adventitia of an arteriole. The vessels were congested. Most of the contained myeloblasts measured 8 or 9μ; but some were smaller, and the mature polymorphonuclear cells measured about 7μ.

OTHER ORGANS.—The intestine showed but little abnormality. One or two myeloblasts were found in the intestinal tissue. Post-mortem autolysis was considerable, and the epithelial layer was missing. The ovaries were normal, except that blood in the vessels showed a great increase in white cells. The uterus was normal. In the suprarenal bodies, the cortex was normal, with some toxic degeneration of cells. Cells of the medulla were diminished, a few were to be found lying in areolar tissue and containing a good amount of yellow pigment. There was no leukæmic infiltration. In the thymus, the medulla showed a little increase in the reticular tissue, and Hassall's corpuscles were slightly diminished in number. Lymphocytes were numerous in the medulla. No leukæmic infiltrations were found. The myocardium showed slight infiltration of myelocytes and metamyelocytes between the fibres. Muscle fibres were well striated.

Discussion.

It is seen from the report of this case that though there was room for speculation during life as to the correct diagnosis, the histological investigations yielded a picture typical of myelosis: yet the last blood count examination, four months before death, revealed only slight evidence of immaturity of the myeloid elements, though the proportion of monocytes was still high (35 per cent.). No increase of monocytes was found anywhere in the tissues, and so no light is thrown on the origin of these cells.

The characteristic picture of monocytic leukæmia shows (a) an increase in the peripheral blood of monocytes or histiocytes (large cells showing pseudopodia, prominent fine granulation, and nuclear complexity and negative oxydase reaction); and (b) a cellular proliferation of reticulo-endothelial cells of the organs containing this tissue; accompanying the proliferation is a widespread infiltration with cells of monocytic characters: large (15 to 40 μ), bulky, pale basophilic cytoplasm, with oval, indented or lobulated streaked nuclei. Against this cellular hyperplasia of the reticulo-endothelium, is its reaction in the spleen and lymph glands in myelosis; here is often seen a more reticular type of proliferation, suggesting an irritative reaction. Moreover, as in this case so also in myelosis, cellular areas of myeloid metaplasia may be found: but interspersed with the swollen reticulo-endothelial cells will be found cells of myeloblastic character, which are distinguishable from those of histiocytes and monocytes.

In the peripheral blood picture of the present case the monocytes were entirely normal in appearance, whereas in our case of monocytic leukæmia[1] recorded elsewhere, they showed pseudopodia, excessive granularity of the cytoplasm, and nuclear complexity—characters regarded as histiocytic by

many. Examination of the white cells present in blood vessels of the tissues showed a great increase in myeloid cells, scarcely any of which appeared to be monocytes. The previous high monocytosis had disappeared at the time of death.

Elsewhere[1] we have referred to the interesting question of the origin of the monocyte, and have suggested that the reticulo-endothelium of lymph glands takes a large share in their production. It is possible that in the present case, the chronicity of the myelosis provided a prolonged stimulus to the lymphatic tissues, thus causing an outpouring of monocytes. Chronic leukæmias are uncommon in children, whose lymphatic systems react strongly; were they more common it is possible that this monocytosis would be found more frequently.

Previous cases.—We have traced the records of several somewhat similar cases in older patients.

Merklen and Wolf[2, 3] have recorded two such interesting cases. Among several others was that of a workman who had the symptoms of acute leukæmia, with ulceration in the mouth, fever, and enlargement of liver, spleen and lymph glands. On admission myeloblasts accounted for 63 and monoblasts and monocytes for 23 per cent. of 200,000 white cells, with similar proportions the day before death. There were multiple leukæmata of the skin and lungs. Histologically, there was myeloid proliferation of the bone marrow, and infiltration of the liver and spleen with large monocytoid cells. There was also hyperplasia of glandular reticulum.

In their other case the spleen was not palpable, and a clinical diagnosis of atypical myeloid or monocytoid leukæmia was made. The white cell count was 28,000, with myeloblasts 28·5, monocytes 24, monocytic cells with very lobulated light nuclei 9, monoblasts 22·8 per cent.; eosinophil cells also were present. This patient improved after X-ray treatment and, in view of the present case, it is interesting to note that fifteen months after the first count the monocytes had practically disappeared, but a high proportion of myelocytes and myeloblasts remained.

Craciuneanu and Calalb[4] have described a case of myelogenous leukæmia with enlargement of the lymphatic glands, in which mononuclear elements, which they regarded as monocytes, appeared in the final stages of the illness. Unfortunately they did not describe these cells in detail nor publish illustrations, and it is quite possible that these cells were myeloblasts, though no doubt their general appearance resembled that of monocytes.

Monocytoid features in myelosis were shown in the cases of Alder[5], Naegeli[6], Ewald, Frehse and Hennig[7], Bykowa[8], Hittmair[9], and Schwarz[10]. In some of these the cells were rather monocytoid myeloblasts than true monocytes.

Differential diagnosis.—It therefore may be accepted that rarely a monocytosis occurs in the course of myelosis, and that in the presence of monocytosis the possibility of underlying myelosis should be borne in mind. At present, it appears impossible to define the characters of the clinical and blood pictures so adequately as to enable a diagnosis to be made with certainty. The other cases quoted showed a marked immaturity of the granulocytes, with definite myeloid leukæmic cells present; but that this immaturity of myeloid elements cannot be relied upon always to reveal itself, is proved by our present case, which showed typical monocytes in large numbers. It is probable that any case of monocytic leukæmia would reveal immature forms of monocytes or histiocytes in the peripheral blood.

Diagnosis from an infective mononucleosis should be easier as that condition, though glandular enlargement is present, shows little diminution in hæmoglobin content and red cell count, great depression of the granulocytes both absolutely and relatively, with little or no immaturity; hepatic and splenic enlargements are not pronounced; above all, there is not the clinical deterioration.

Conditions such as malaria and kala azar show less marked monocytic reactions, and other features which should prevent confusion with a leukæmic process. Agranulocytic angina shows necrosis of the pharynx, and a blood picture almost lacking in any myeloid elements and usually without a monocytosis.

Reference to the records has revealed that most authentic cases of monocytic leukæmia or leukæmic reticulo-endotheliosis show almost an entire absence of eosinophil cells from the peripheral blood stream (Ugriumow[11], Boch and Wiede[12], Hittmair[9], Hannema[13]); whereas, as is well known, these cells are common in myelosis. The eosinophil count may therefore be an indication; in the present case it points against monocytic leukæmia.

The following conditions have been recorded as showing monocytosis of leukæmic or aleukæmic type:—

(1) Monocytic (or histiocytic) leukæmia (Clough[14]).

(2) Leukæmic reticulo-endotheliosis (Boch and Wiede[12], Gittins and Hawksley[1]). Both of these are rare conditions.

(3) Monocytic reactions in myelosis (Merklen and Wolf[2, 3]).

(4) Monocytoid cells regarded as types of myeloblasts in myelosis (Hittmair[9]).

Further, some cases have recently been described, mainly by German workers, in which there is usually no monocytosis in the blood stream, but which show limited or widespread reticulo-endothelial hyperplasia of a cellular type, and are possibly due to infective processes (Tschistowitsch and Bykowa[15], Akiba[16]). The relationship of these conditions is discussed above.

Our present case falls under the third heading of the above list.

Summary.

A case of prolonged monocytosis in a child, shown at autopsy to be incidental in the course of a chronic myelosis, is recorded.

Brief reference is made to similar conditions and their relation to monocytic and histiocytic leukæmia and leukæmic reticulo-endotheliosis is discussed.

REFERENCES.

1. Gittins, R., & Hawksley, J. C., *J. Path. & Bact.*, Edinb., 1933, XXXVI, 115.
2. Merklen, P., & Wolf, M., *Presse méd.*, Paris, 1927, XXXV, 145.
3. Merklen, P., & Wolf, M., *Rev. de méd.*, Paris, 1928, XLV, 153.
4. Craciuneanu, A., & Calalb, G., *Sang*, Paris, 1931, V, 397.
5. Alder, A., *Folia hæmat.*, Leipsic, 1923, XXIX, 105.

6. Naegeli, A., *Blutkvaukheiten & Blutdiagnostik.*, Berlin, 1923.
7. Ewald, Frehse, & Hennig, *Deutsch. Arch. f. Klin. Med.*, Leipsic, 1922, CXXXVIII, 353.
8. Bykowa, O., *Folia Hæmat.*, Leipsic, 1930, XLIII, 475.
9. Hittmair, A., *Ibid.*, 1930, XLII, 271.
10. Schwarz, E., *Ibid.*, 1931, XLIV, 332.
11. Ugriumow, B., *Zentralb. f. Allg. Path. u. Path. Anat.*, 1928, XLII, 103.
12. Boch, H. E., & Wiede, K., *Virch. Arch. f. Path. Anat.*, Berlin, 1930, CCLXXVI, 553.
13. Hannema, L. S., *Nederl. Tijdschr. v. Geneesk*, Haarlem, 1928, LXXII, 2281.
14. Clough, P. W., *Bull. Johns Hopkins Hosp.*, Baltimore, 1932, LI, 178.
15. Tschistowitsch, T., & Bykowa, O., *Virch. Arch. f. Path. Anat.*, Berlin, 1928, CCLXVII, 91.
16. Akiba, R., *Ibid.*, 1926, CCLX, 262.

FACTORS CAUSING VARIATION IN THE HÆMOGLOBIN LEVEL WITH AGE IN THE FIRST YEAR OF LIFE

BY

HELEN M. M. MACKAY, M.D., M.R.C.P.
(From the Queen's Hospital for Children and the Mothers' Hospital, London.)

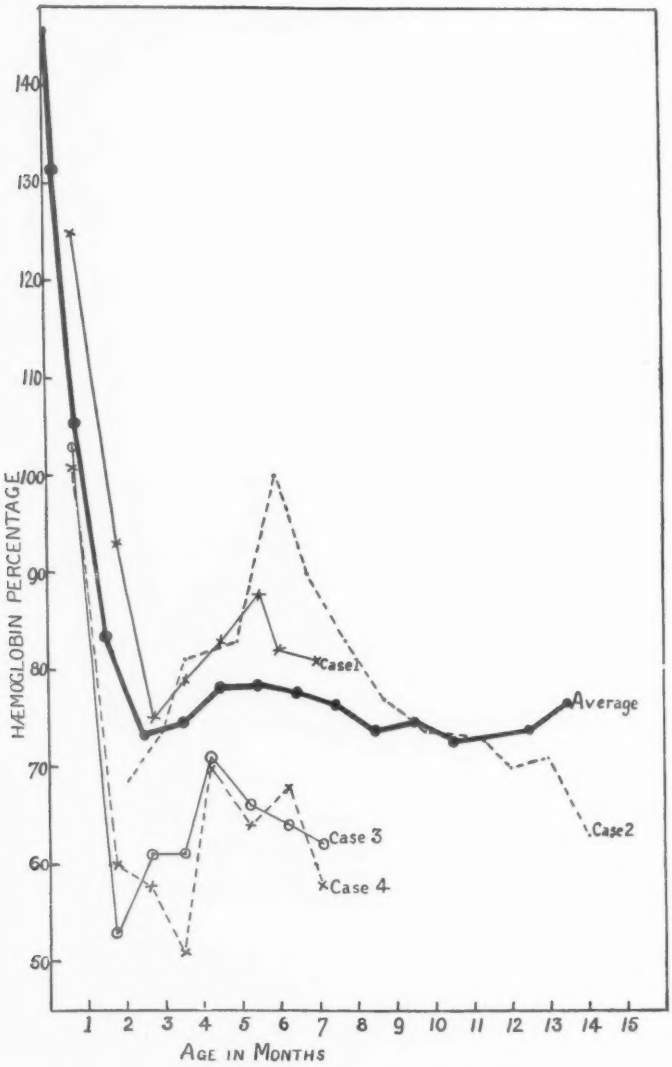
The hæmoglobin level of infants during the first year of life usually shows certain clearly marked phases. These are:—a sharp drop from the high level at birth to a figure in the neighbourhood of half this value by the third month of life; a rise from this age till the sixth month of life; a second fairly steady fall continuing until after mixed feeding has been started, and then a slow and rather irregular rise[19]. It is the purpose of this paper, by bringing together our own results and those of other investigators, to show, or suggest, a sequence of causes producing these changes in hæmoglobin level. Many of the conclusions reached, however, must at present be regarded as tentative.

Average curve for first year.—First let us consider in greater detail the ordinary hæmoglobin curve for the first year of life for a breast-fed baby (Graph I). The absolute hæmoglobin values are of minor importance for our present purpose, since they may vary greatly in individuals as well as with different technique for estimation, but changes in level occur at similar ages in nearly all babies and it is on these we now wish to concentrate*.

At birth the hæmoglobin percentage averages, according to our data, about 146; it then drops rapidly, especially during the first week of life, so that by one week old it reaches 131, and by 2 to 3 months old 73. For the next three months it is usually rising, reaching an average level of 78 at 5 to 6 months old. Then it drops slowly till it reaches 73 at 10 to 11 months. It should be noted that these figures are average values, and consequently do not show the magnitude of the rise and fall in level commonly met in individuals. For example, the rise (without treatment) between about the third month and the sixth month of life is fairly frequently 15 per cent., and may be over 25 per cent. (Graph I, Cases 1–4; Graph II, Case 6); but because of the varying ages at which the rise begins and ends (or in other words the varying ages at which the highest and lowest levels occur in different individuals), its extent is masked by taking an average figure for each month of life. These figures refer to breast-fed babies without any infections.

* All figures for the author's cases quoted in this paper are in terms of the Price-Jones—Haldane hæmoglobinometer standard. The calculation of figures based on this standard from those we have previously published is discussed in a preceding paper[20].

Artificially fed babies show a similar type of hæmoglobin curve, but the average figures are slightly lower.



GRAPH I.—Average hæmoglobin curve for breast-fed babies for the first year of life, with curves from untreated infants (Cases 1—4).

CASE 1.—A full-term baby showing a drop of 50% between $\frac{3}{4}$ and $2\frac{3}{4}$ months old; a rise of 13% between $2\frac{3}{4}$ and $5\frac{1}{2}$ months; and a subsequent fall. A typical case, excepting that at $\frac{3}{4}$ month the level was higher than usual.

CASE 2.—A full-term baby showing a rise of 32% between 2 and 6 months of age, and a drop of 37% between 6 and 14 months. In this case both rise and fall were considerably greater in extent than usual.

CASE 3.—A twin weighing 4 lb. 11 oz. at birth, and with a hæmoglobin level always below the curve for the average, but rising by 18% between $1\frac{3}{4}$ and $4\frac{1}{4}$ months

CASE 4.—Twin to Case 3., weighing 3 lb. 13 oz. at birth, and tending to have a hæmoglobin level rather lower than his brother who was heavier at birth. He shows a rise of 19% in 3 weeks, reaching 70% at $4\frac{1}{4}$ months.

Any severe infection is likely to lower the hæmoglobin level; the type of anæmia thereby produced appears as a rule to be hæmolytic[14], i.e., an anæmia due to increased blood destruction. On recovery from the infection there is a tendency to spontaneous improvement in the hæmoglobin level, provided other factors are favourable. It seems that the existence of an infection may postpone the rise in hæmoglobin level which generally occurs in the second three months of life.

The average level at birth and variation with birth weight.—Our average percentage figure for hæmoglobin level at birth of healthy infants is approximately 146, with a maximum value of 179 and a minimum value of 110. If we group the babies by birth weight (Table 1), the 5-lb. babies

TABLE 1.

BIRTH WEIGHT AND HÆMOGLOBIN IN FIRST WEEK.

Birth weight.	Average hæmoglobin percentage.		Drop in first week.
	Under 24 hours.	8th day.	
5 lb. odd ...	158·5 (12)	137·7 (10)	20·8
6 lb. ,, ...	148·2 (14)	128·0 (13)	20·2
7 lb. ,, ...	141·0 (22)	129·4 (20)	11·6
8 lb. and over ...	139·8 (14)	133·0 (12)	6·8
5-9 lb. combined ...	145·7 (62)	131·4 (55)	14·3
6 lb. and upwards combined ...	142·7 (50)	129·9 (45)	12·8

Figures in brackets indicate the number of healthy babies examined.

average 158·5, and there is a serial drop in hæmoglobin level with increasing weight until we reach the babies of 8 lb. and upwards who average 139·8, or about 19 per cent. lower.

These figures suggest that each pound increase in birth weight is accompanied by a corresponding decrease in the average hæmoglobin level. Roughly speaking, the higher the birth weight the lower the average hæmoglobin level at birth and vice versa, though individuals vary widely. Unfortunately we have no figures for the average hæmoglobin level at birth of babies weighing under 5 lb., and although various authors[2] have stated that the hæmoglobin level at birth of premature babies is higher than in full term infants, we have not been able to discover any entirely satisfactory comparative figures.

CAUSE OF THIS VARIATION.—Table 1 shows the new-born babies in our series arranged in groups of similar birth weight. Since all the babies were healthy infants in one maternity hospital, it seems legitimate to assume that the higher the birth weight the greater the average intra-uterine age, or at least the greater the average degree of maturity at birth. If this be so, then the more mature new-born babies have a lower hæmoglobin level than the less mature; so either blood production diminishes or blood destruction increases in late intra-uterine life. Probably both factors play a part.

To consider blood production first:—In the fœtus of 4 to 6 months, the number of immature red cells, e.g., nucleated cells and reticulocytes, is very

large[25], and presumably blood formation is rapid to keep pace with the rapid growth of the fœtus. The reticulocytes and nucleated cells present in the full term baby at birth, though much in excess of adult figures[4, 25], are far fewer than in the young fœtus, and considerably fewer than in the premature babies[2]. If we assume that the number of reticulocytes in circulation is a rough indication of the rate of blood production, these facts suggest, as might be expected, that the rate of new red-cell formation is slowing down with the diminished rate of growth as the age of the fœtus increases. Nevertheless, there is also evidence to suggest increased blood destruction. In hæmolytic anæmias, as is well known, the bilirubin in the blood is raised as a result of hæmolysis. In the umbilical vein at birth (whether the infant is delivered by the normal passages or by Cæsarian section), the bilirubin is very much higher than in adult blood. Hampson[10] finds an average of 1 in 75,000 in fœtal blood as compared with 1 in 400,000 in adult blood; and his figures suggest, though the total number of premature infants and fœtuses examined was not large, that between 14 weeks' gestation and term the bilirubin in the fœtal blood steadily increases. His figures are:—14 weeks fœtus, no bilirubin in blood plasma; 20 weeks fœtus, bilirubin definitely present; 28 weeks, marked positive van den Bergh; 34 weeks, bilirubin 1 in 150,000; 36 weeks (2 cases), bilirubin 1 in 130,000 and 1 in 120,000; 38 weeks, bilirubin 1 in 100,000; and at full term, bilirubin 1 in 75,000. Hence there seems little doubt that during the latter part of pregnancy there is increased fœtal blood destruction. If we assume that the high hæmoglobin level at birth is necessitated by the low oxygen tension of fœtal blood, and the drop after birth is in response to a sudden rise in oxygen tension at this time, then it seems legitimate to suppose that the probable explanation of the increased hæmolysis which apparantly occurs during late intra-uterine life is a gradual improvement in the oxygenation of the fœtal blood during this period. Whether there is any anatomical or experimental evidence to support the suggestion the author has not discovered.

Fall in first three months : variation with birth weight.—During the first 6 weeks of life the drop in red cell count and hæmoglobin level is usually rapid. It is generally most rapid in the first week, the average drop for our cases being 14 per cent. by the eighth day. Schiff[26] in Grosswardein found an average drop of 26 per cent. during the same period; Zibordi[31] 17 per cent.; and Lucas[18] and his co-workers 14 per cent. The extent of the fall shows wide individual variations: the maximum in our series was 44 per cent. in one week in an apparently normal baby, but, on the other hand, several had at one week old a hæmoglobin level approximately equal to that at birth.

The fall in hæmoglobin level reflects the drop in the red-cell count: Lucas[18] and his co-workers found in the first week of life a drop of about one million cells, i.e., from 5,511,000 per c.mm. at birth (31 cases) to 4,504,000 (19 cases) on the eighth day. Mayers'[23] figures indicate in the first two weeks a drop of nearly two million cells: from 7,630,000 at birth (41 cases) to 5,790,000 (10 cases) on the 14th day.

The fall in hæmoglobin percentage, with individual exceptions, is usually greater in the smaller babies. In our series in those of 5 lb. birth weight it averaged about 21 in the first week; in those of 6 lb. 20; in those of 7 lb. 12; and in those of 8 and 9 lb. only about 7 (Table 1). By the third month 5 lb. babies had dropped by about 90, and babies of 8 lb. and upwards by 66 per cent. (see Tables 2 and 3). The rapid drop shown by small premature babies

TABLE 2.

BIRTH WEIGHT AND HÆMOGLOBIN AFTER FIRST TWO WEEKS: AVERAGE FOR BREAST-FED AND ARTIFICIALLY-FED BABIES COMBINED.

Birth weight.	½-1 month	1-2 months	2-3 months	5-6 months	10-11 mths.
3 lb. odd ...	—	62·0 (1)	51·0 (1)	64·0 (1)	49·0 (1)
4 lb. ,, ...	—	73·0 (1)	58·3 (4)	61·9 (6)	48·4 (3)
5 lb. ,, ...	109·1 (2)	78·1 (11)	68·9 (22)	75·5 (20)	65·8 (7)
6 lb. ,, ...	105·8 (9)	83·2 (32)	71·9 (38)	75·1 (39)	71·7 (25)
7 lb. ,, ...	105·2 (12)	81·0 (35)	73·6 (38)	78·1 (51)	74·7 (31)
8 lb. and upwards	105·7 (8)	84·8 (27)	73·8 (55)	79·4 (42)	72·2 (36)

Figures in brackets indicate the number of babies examined.

TABLE 3.

BIRTH WEIGHT AND DROP IN HÆMOGLOBIN BETWEEN BIRTH AND LATER INFANCY.

Birth weight	Hæmoglobin at birth	Drop in hæmoglobin percentage at various months.				
		½-1 m.	1-2 m.	2-3 m.	5-6 m.	10-11 m.
5 lb. odd ...	158·5	49·4	80·4	89·6	83·0	92·7
6 lb. ,, ...	148·2	42·4	65·0	76·3	73·1	76·5
7 lb. ,, ...	141·0	35·8	60·0	67·4	62·9	66·3
8 lb. and upwards	139·8	34·1	55·0	66·4	60·4	67·6

is well known. Thus babies of low birth weight do not continue to have high hæmoglobin levels; on the contrary, the order is likely to be reversed as compared with that at birth, and by 2 to 3 months old babies of lowest birth weight have the lowest hæmoglobin levels, and the higher the birth weight the higher is likely to be the average hæmoglobin percentage[19]. The low levels usually reached by small premature infants at 2 to 3 months old is shown by Lichtenstein's[17] average of 40 per cent. hæmoglobin and red cells under 3,000,000, based on 30 infants; or by Kunckel's[15] figure of approximately 46 per cent. hæmoglobin for 21 infants whose birth weight averaged 4 lb. odd. These figures for the hæmoglobin of premature babies in the third month of life are 27 to 33 per cent. below our figures for the average hæmoglobin value of breast-fed infants at that age.

THE CAUSE OF THE FALL IN THE FIRST WEEK OF LIFE.—It is generally agreed that the high initial hæmoglobin level at birth is associated with the poor oxygenation of the arterial blood of the fœtus in utero, due to the inferiority of the placenta to the lung as a medium for oxygenation and to the mixing of arterial and venous blood. After birth the number of red cells

is reduced by hæmolysis, and in every baby, whether or not the skin shows the icteric tinge of so-called physiological (hæmolytic) jaundice, there is in the early days of post-natal life a sharp rise in the bilirubin of the blood[8, 10] resulting from the breakdown of corpuscles. This rise reaches its maximum in most babies about the third day[10] or fourth day[18]; but in infants in whom the rise is high the apex of the curve is reached considerably later[10]. The work of Goldbloom and Gottlieb[6, 7, 8] is of interest in this connection. They showed that the sequence of changes in the blood of new-born infants can be reproduced in laboratory animals. They first demonstrated by direct measurement the low oxygen tension of fœtal blood[6]. They next placed guinea pigs in the laboratory under reduced atmospheric pressure[7] and produced in them a reticulocytosis and the expected rise in red cells and in hæmoglobin level, corresponding with the changes in the blood found in persons becoming acclimatized to high altitudes. They then increased the atmospheric pressure to normal, so producing a rise in the oxygen tension of the blood. The result was a rapid fall in the red cells and hæmoglobin which reached normal in five days, and a corresponding rise of bilirubin in the blood, showing that the reduction in red cells was brought about by hæmolysis.

The mechanism of the blood destruction occurring after birth does not appear to be clearly understood. Hampson[10] has found that in the new-born infant there is a much larger difference between the pH of the red cell and the pH of the plasma, than there is in the normal adult. A similar striking difference in pH is found in certain hæmolytic anæmias[9], for example, in acholuric family jaundice; and Hampson believes that the chemical mechanism of destruction of the red cells in the new born is connected with this difference in chemical reaction between cells and plasma.

Some of the red cells of the new-born infant are more fragile, that is more easily hæmolyzed in hypotonic saline, than are the cells of a normal adult. The blood of a full-term new-born infant begins to hæmolyze according to Hampson[10] with a 0·525 per cent. hypotonic saline which causes no hæmolysis of red cells of the normal adult. On the other hand, hæmolysis in both infant and adult is complete in saline of the same strength, i.e., 0·3 per cent. In a premature baby some of the red cells are still more easily hæmolyzed, and in a 14-weeks fœtus hæmolysis began in 0·70 per cent. saline, but was not complete except in saline dilute enough to produce complete hæmolysis in adult blood[10]. At birth, as already mentioned, there are immature erythrocytes in circulation, namely, nucleated red cells and reticulocytes. Goldbloom and Gottlieb[8] have shown that immature cells are the most easily hæmolyzed in hypotonic saline solution. Premature babies have more of these immature cells in circulation than full-term babies; hence the more rapid the fall in their red cells is presumably, at least in part, the result of the greater proportion of immature cells in their blood.

The possible influence of an anti-hæmolytic hormone in controlling the rapidity of the initial drop in red cells is of considerable interest. Hampson[10] suggests that the mother's liver may normally provide the fœtus with such

a hormone before the infant's own liver takes on this function, and that physiological jaundice is due to the inefficiency of the liver of the new-born child (a) to provide a secretion preventing hæmolysis, and (b) to excrete the bilirubin. van Creveld and Heybroek[30] have shown that for equal falls of erythrocytes from birth the icteric index is variable; hence efficiency in the removal of bile substances from the blood evidently varies in the new born. Hampson also suggests that grave familial jaundice of the new born may be due to ' further delay in the assumption of hepatic efficiency,' and that it is a pathological exaggeration of the ordinary physiological (hæmolytic) jaundice. Hampson [10, 11] has demonstrated conclusively that injection of the serum of a normal adult into an infant suffering from this form of jaundice with anæmia will usually cure: hence it seems probable that the adult serum supplies the infant with some factor controlling hæmolysis. Moreover, in one case of familial icterus gravis neonatorum he showed that the fragility curve of the red blood cells was of the infantile type, but showed hæmolysis in excess of the average for the new born; whereas on mixing the infant's cells with adult serum (his own or the mother's), he diminished hæmolysis and obtained a curve which approximated to the adult type. It seems probable that injection of adult blood will also arrest hæmolysis in so-called congenital anæmia of the new born[22], a condition apparently closely related to familial icterus gravis. Thus there is a good deal of evidence to support his hypothesis of an anti-hæmolytic hormone which normally prevents excessive blood destruction in the new-born child. However, it seems the problem cannot yet be considered definitely settled, since Goldbloom and Gottlieb[8] have been unable to demonstrate any anti-hæmolytic agent in the mother's blood when her serum is added to the washed corpuscles of the infant.

Causes of the fall between one week and three months.—By one week old the more fragile cells in the blood have apparently been destroyed, for by this age the hæmolysis curve of the infant's corpuscles in hypotonic saline approximates to the curve for adult blood[8]. But, as already shown, the red cell and hæmoglobin level continue to fall until about the third month of life and in many cases, especially in babies small at birth, reaches levels so low that they must be considered pathological. Is, then, this continued fall due to continued blood destruction, or is it due to diminished blood production, or to both? Hampson[10] finds excess of bilirubin in the blood until one month of age, and the figures given by Lucas and his co-workers suggest that in some babies the fall in bilirubin may be slower. Hence excessive blood destruction presumably continues throughout the first month.

For evidence of activity in the blood-forming organs we may consider the number of reticulocytes in the blood. At birth it is agreed that this is high, but within one or two weeks after birth the number has dropped to a figure approximating to that for adult blood[4, 25], and apparently remains fairly stationary until the fourth week. Thereafter, from the fifth to the

eighth week it rises steadily[24]. van Creveld and Heybroek[30] find a similar fall and subsequent rise in the reticulocytes of premature babies. This appears to support the view that during the first month of life the rate of blood production is normally much diminished, but that after this time it again increases. Schiff and Joffe[27] give some interesting figures for three premature babies. These babies were treated with copper, but if we assume that copper given alone was without effect on the red cells (and such an assumption seems justified by the work of Josephs[13] and others), we can regard these as untreated cases. In the first month of life the percentage of reticulocytes in the blood of these infants was 12 to 10, but between $1\frac{1}{2}$ to 2 months old it rose as high as 23 to 40, suggesting that during this time, when in each baby the red cells and hæmoglobin percentages were dropping, the organism was making a great effort to balance this excessive blood destruction. Moreover the following case suggests that if the rate of blood destruction is far in excess of normal during the early weeks of life, blood production will continue from birth onwards, at a high level to make good the excessive destruction. The case was one of icterus gravis neonatorum observed by Ockel[25], and the reticulocytes were maintained at a similar level to that at birth until the eighteenth day when the child died. Similar high reticulocyte counts in icterus gravis are quoted by other authors. Contrast this with the figure for normal babies in whom Friedlander and Wiedemer[1] find about 14,000 to 28,000 reticulocytes per c.mm. at birth and 0 to 25 by the ninth day. The above findings taken together suggest that (a) the drop in hæmoglobin from birth to about the third month is primarily due to destruction of red cells; but that (b) normally during the first month when the cells are presumably in excess of the body's requirements and hæmolysis is physiological, cell production is diminished; and that (c) after the first month cell production again increases, though it does not usually balance destruction until the third month of life. If, however, in the first weeks of life destruction produces a red-cell level which is pathologically low, increased production comes into play at once.

Trought[29] has demonstrated an interesting fact about the hæmoglobin of new-born infants. The hæmoglobin of the new born, or a proportion of it, differs in chemical composition from the hæmoglobin of the human adult, and this embryonic type of hæmoglobin continues to be present in the blood until at least $1\frac{1}{2}$ months of age, and perhaps longer, as her series contained no babies between $1\frac{1}{2}$ and $4\frac{1}{2}$ months of age. By $4\frac{1}{2}$ months all the hæmoglobin is of the adult type. The significance of this observation is not yet known. It may be that blood destruction continues until the body is rid of the whole of the embryonic hæmoglobin. In favour of this view is the fact that the embryonic hæmoglobin is present during the period after birth when hæmolysis outstrips blood formation; whereas, by $4\frac{1}{2}$ months old, when the normal red cell building has outstripped destruction, the whole of this embryonic hæmoglobin has been replaced by the adult type.

It seems unlikely that the drop in red cells in the first two to three months of life is associated with any nutritional deficiency: some writers[16] have claimed to improve the hæmoglobin level in the second and third months of life by giving iron, but satisfactory proof of this is wanting[30]. Moreover, if iron or any other nutritional deficiency, were a limiting factor at this age, it seems probable that the babies who grown most rapidly would show the most marked deficiency, and hence the lowest hæmoglobin levels. But Dr. Bradford Hill[19] examining our data, could find no statistical evidence to indicate this, that is he failed to find any correlation between rate of growth (for constant birth weight) and the hæmoglobin level at $2\frac{1}{3}$ to $3\frac{1}{3}$ months old. Two other facts which also contra-indicate any theory of iron deficiency are: first, that recent investigations have shown that the iron store in the liver increases up to two months of age[5] (see next section); and secondly, that if anæmia develops in the first three months of life it is characterized by a reduction in red cells and in hæmoglobin alike[17], and is not of the chlorotic type usually associated with iron deficiency.

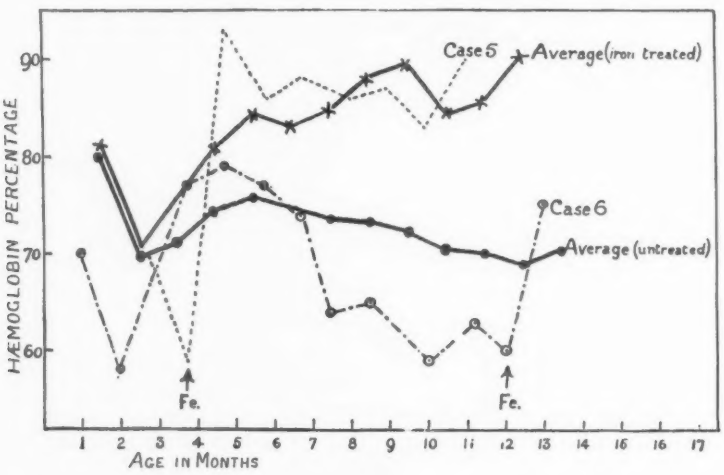
The problem of abnormally low hæmoglobin levels in the first three months of life would be simplified by finding an effective means of prophylaxis. Abt and Reynolds[1] claim that iron together with a ' secondary anæmia liver extract ' (prepared as suggested by Whipple and Robbins) is of prophylactic value in the anæmia of premature babies in the first half year of life; but its effect during the first three months is not established by their published data, and after three months of age we know that iron alone begins to show its prophylactic value in some infants (Graph II).

It is evident that further information about the drop in hæmoglobin level in the first three months of life is required. This might be obtained by studying the possible prophylactic value of injections of adult blood. Such an investigation is now being carried out.

Rise between the third and sixth month.—Whatever factors may control the rapid diminution in red cells in the early weeks of life, they are usually checked at two or three months of age; and even in premature infants and small twins (Graph I, Cases 3 and 4), from about this age red-cell formation outstrips destruction and more than keeps pace with the growth of the infant. Thus from about the third to the sixth month there is, in nearly every infant, a rise in the hæmoglobin level and a proportionately greater rise in the red-cell count. Lichtenstein's[17] series of premature babies showed between the third and sixth months an average rise of nearly two million in the red cells, and by six months old they were suffering from an anæmia of the chlorotic type because red-cell formation had outstripped hæmoglobin formation.

In this connection the work of Gladstone[5] is of great interest. He found that from two weeks to two months of age there is an accumulation of iron in the infant liver and spleen over and above the store present at birth, but

after this age the excess diminishes and by four months of age has disappeared. The inference seems clear. The infant organism has been conserving from the early weeks of life iron and possibly other products of the breakdown of corpuscles, and as soon as the causes producing a fall in hæmoglobin level are checked, this iron is steadily transferred from the depots in liver and spleen to the new red-blood corpuscles which are being put into circulation, and somewhere round the third month the hæmoglobin level begins to mount. By four months of age, however, the obvious excess of iron has disappeared from the liver, and since the infant's diet, namely milk, is very poor in iron a deficiency of this substance is likely to occur with a consequent check in the rise of the hæmoglobin level soon after the store has given out. Sometimes the need for extra iron occurs as early as three months, for iron treatment begun under two months will produce in the fourth month a higher average hæmoglobin level than is found in untreated babies (Graph II). Iron administration will in many infants accelerate and increase the rise ordinarily occurring without treatment after the third month, and with such treatment a rise of over 30 per cent. may sometimes occur in one month (Graph II, Case 5).



GRAPH II.—Average hæmoglobin curves for artificially-fed babies for the first year of life: (a) untreated, and (b) treated with iron from under 2 months old; with (c) hæmoglobin curves Cases 5 and 6.

CASE 5.—Full-term baby given iron from $3\frac{3}{4}$ months when his hæmoglobin was 59%. The iron presumably accelerated the expected rise since there was subsequently a rise of 34% in 4 weeks, and the hæmoglobin thereafter remained near 86% as a result of continuous iron treatment.

CASE 6.—A full-term baby showing a rise of 21% between 2 and $4\frac{3}{4}$ months old without treatment, and thereafter a fairly steady fall till 10 months old. The fall was arrested between 10 and 12 months old, presumably as a result of a mixed diet, and the administration of an iron salt at 12 months of age caused a sharp rise.

The fall in hæmoglobin after five months.—Without iron treatment the initial rise is usually followed at about six months of age by a slow fall in hæmoglobin level (Graph I), which continues until iron is supplied to the

baby (Graph II, Case 6). On the other hand, with regular iron treatment the hæmoglobin level can be kept in the neighbourhood of 86 per cent. provided the child is not ill (Graph II, Case 5). If the baby has grown quickly relative to its birth weight, if, for instance, this has been trebled instead of doubled by five or six months of age, then its iron store is exhausted earlier. By the statistical analysis of our figures for breast-fed babies, Dr. Bradford Hill[19] has shown that from 6 to 12 months old the hæmoglobin level is correlated with the rate of growth; babies who have made the largest percentage increase in weight over their birth weight tend to have the lowest hæmoglobin levels. Rapid growth together with presumably excessive hæmolysis in the first two months of life are almost certainly the main causes predisposing to nutritional anæmia in babies small at birth; they grow relatively faster than babies of higher birth weight, and consequently exhaust their iron store earlier, and so may show the effects of iron deficiency from any age after about three months. Ante-natal iron deficiency in the mother is another cause of early exhaustion of the iron store in the infant, with consequent anæmia[28].

So far no account has been taken of the possible part played by copper and other mineral or organic deficiencies in this common nutritional anæmia of babies. This must not be taken to imply that iron is always the only deficiency, but, as shown in another paper[21], there are reasons for supposing that copper deficiency is seldom present in the nutritional anæmia in babies. The fact that large doses of inorganic iron, far in excess of the amount utilized by the baby, are desirable in treatment, is apparently due to deficient absorption[12].

This is not the place to discuss the relatively uncommon type of nutritional anæmia due to deficiency of vitamin C, nor of the forms of anæmia, probably partly nutritional in origin, which may arise as a result of lesions affecting the digestive tract, nor again of the anæmia associated with deficiency of internal secretion from the thyroid gland; but, of course, any of these may occur in infancy and complicate the picture already described.

The rise in hæmoglobin on a mixed diet.—In our study of nutritional anæmia in infancy we found that towards the end of the first year of life a certain number of infants showed a slow and usually irregular rise in their hæmoglobin level. This is evidently due to their receiving a mixed diet and thus considerably increasing their iron intake. It is worth noting, however, that the rise in hæmoglobin level on an ordinary mixed diet is often delayed, and is, moreover, greatly inferior to that usually obtained by giving an inorganic iron salt[19].

Elvehjem[3] has drawn attention to the inferiority of organic iron to inorganic iron in the treatment of ' milk anæmia ' in the rat, and this accords with our general observations in children. On the other hand,

treatment with liberal amounts of liver may produce very good results[19], though the amount of iron supplied is only a fraction of that ordinarily prescribed in the form of a drug. This may indicate that liver supplies some other factor which augments the effect of the iron it contains, or it may simply mean that iron present in liver is in an easily utilizable form.

Conclusions.

An attempt has been made from the data available to relate the usual variations in hæmoglobin level during the first year of life to their causal factors. Some of the conclusions are tentative, but the suggested hypotheses may serve to stimulate further investigation.

The high hæmoglobin level of the new-born infant is known to be related to the low oxygen tension of the blood of the fœtus in utero[7] and its consequent need of a relatively greater amount of hæmoglobin. Hæmolysis of red cells apparently exceeds red-cell formation during late intra-uterine life, as shown by the presence in the new-born infant's blood of bilirubin considerably in excess of adult figures[8, 10]; and the fact that infants larger, and presumably more mature, at birth tend to show on the first day of life lower hæmoglobin percentages in their blood than do smaller infants. Increasing the oxygen tension of the blood has been shown to produce in animals a drop in red-blood cells with a rise in bilirubin[7], which suggests that this intra-uterine hæmolysis may run parallel with improving oxygenation of the fœtal blood during the latter part of intra-uterine life. The rate of red blood cell production presumably decreases during the latter part of fœtal life since reticulocytosis diminishes towards term[25].

After birth there is a fairly rapid destruction of red cells, the more fragile immature cells[8] which are present in greater proportion in the blood of immature infants, being early destroyed. Hence there is a rapid fall in hæmoglobin in the first week of life, greatest in infants of low birth weight, and less in infants of higher birth weight. This destruction causes a further increase in blood bilirubin[10, 17], and may give rise to an icteric tinge to the skin, namely ' physiological ' jaundice. During this stage of physiological blood destruction, red-cell building is presumably decreased as shown by the small number of retioculocytes in the blood of normal infants between one and four weeks old[24]. The drop in red cells continues until about the third month of life. The meagre evidence available seems to point to red-cell building again increasing between five and eight weeks old, though it does not usually exceed destruction till the third or fourth month. Red-cell hæmolysis of a pathological grade in the first weeks of life may call out a counteracting increase in red-cell production.

If we neglect cases of icterus gravis neonatorum, and the severe hæmolytic anæmia of the new born which is probably closely related to it, no effective method of treatment has yet been found to check an excessive

drop in hæmoglobin level between birth and two or three months of age, e.g., a drop to less than 50 per cent., such as may not infrequently be seen in premature infants.

Iron derived from hæmolysis of red cells in the early weeks of life augments the original store present in the liver and spleen at birth[5], and is utilized during the period of a rising hæmoglobin level, namely between about the third and sixth month of life. This store, however, quickly becomes depleted, especially in infants whose rate of growth has been rapid; and consequent iron deficiency often retards the rise and usually causes a slow drop in hæmoglobin level after the sixth month of life. Towards the end of the first year of life a slow spontaneous rise in hæmoglobin level may again occur, resulting from increased iron intake due to a mixed diet.

The author offers her thanks to the Medical Research Council for a personal grant which allowed her to carry out her investigations. She is also much indebted to Miss Lorel Goodfellow for her constant help.

POSTSCRIPT.—Since this paper was written Professor L. G. Parsons and his colleagues have published their important studies in anæmia in this journal, and have had under consideration many of the points discussed in the present paper. Nevertheless it is hoped that the present survey may prove useful and may supplement in certain respects the valuable papers from the Birmingham Children's Hospital.

H.M.M.M.

REFERENCES.

1. Abt, A. F., & Reynolds, N. B., *J. Am. Med. Ass.*, Chicago, 1932, XCVIII, 2270.
2. Baar, H., & Stransky, E., *Die klin. Hämatol. d. Kind.*, Leipzig, 1928, 9.
3. Elvehjem, C. A., *J. Am. Med. Ass.*, Chicago, 1932, XCVIII, 1047.
4. Friedlander, A., & Wiedemer, C., *Am. J. Dis. Child.*, Chic., 1925, XXX, 804.
5. Gladstone, S. A., *Ibid.*, 1932, XLIV, 81.
6. Goldbloom, A., & Gottlieb, R., *J. Clin. Invest.*, N.Y., 1930, IX, 139.
7. Goldbloom, A., & Gottlieb, R., *Ibid.*, 1930, VIII, 375.
8. Goldbloom, A., & Gottlieb, R., *Am. J. Dis. Child.*, Chic., 1929, XXXVIII, 57.
9. Hampson, A. C., & Maizels, M., *J. Physiol.*, Cambridge, 1927-8, LXIV, (*Proc. Phys. Soc.*), xx.
10. Hampson, A. C., *Guy's Hosp. Rep.*, Lond., 1928, LXXVIII, 199.
11. Hampson, A. C., *Lancet*, Lond., 1929, I, 429.
12. Heath, C. W., Strauss, M. B., & Castle, W. B., *J. Clin. Invest.*, N.Y., 1932, XI, 1293.
13. Josephs, H., *Bull. Johns Hopkins Hosp.*, Baltimore, 1931, XLIX, 246.
14. Josephs, H., *Ibid.*, 1932, LI, 185.
15. Kunckel, D., *Ztschr. f. Kinderh.*, Berlin, 1916, XIII, 101.
16. Landé, L., *Ibid.*, 1926, XLII, 349.
17. Lichtenstein, A., *Svenska läk.-sällsk.*, Stockholm, 1917, XLIII, 1824.
18. Lucas, W. P., et al., *Am. J. Dis. Child.*, Chic., 1921, XXII, 525.
19. Mackay, H. M. M., & Goodfellow, L., *Med. Res. Council, Sp. Rep. Ser.*, Lond., 1931, No. 157.
20. Mackay, H. M. M., *Arch. Dis. Childh.*, Lond., 1933, VIII, 221.
21. Mackay, H. M. M., *Loc. cit.*, 145.

22. Mackay, H. M. M., *Proc. Roy. Soc. Med.*, Lond., 1933 (in press).
23. Mayers, L. H., *Arch. Int. Med.*, Chicago, 1922, XXX, 478.
24. Ockel, G., *Münch. med. Wchnschr.*, Munich, 1924, LXXI, 1356.
25. Ockel, G., & Haagen, W. W., *Arch. f. Kinderh.*, Stuttgart, 1927, LXXX, 107.
26. Schiff, E., *Jahrb. f. Kinderh.*, Berlin, 1901, LIV, 1, 172.
27. Schiff, E., & Joffe, N., *Klin. Wchnschr.*, Berlin, 1931, X, 1946.
28. Strauss, M. B., *J. Clin. Invest.*, N.Y., 1933, XII, 345.
29. Trought, H., *Arch. Dis. Childh.*, Lond., 1932, Vll, 259.
30. van Creveld, S., & Heybroek, N., *Rév. franç. péd.*, Paris, 1932, VIII, 158.
31. Zibordi, F., Quoted by Baar and Stransky[2].

RENAL RICKETS ASSOCIATED WITH PARATHYROID HYPERPLASIA

BY

F. S. LANGMEAD, M.D., F.R.C.P.,

AND

J. W. ORR, M.D., B.Sc.

(From St. Mary's Hospital, London.)

The clinical picture presented by cases of renal dwarfism is well recognized, but there remains some uncertainty concerning the bony changes which form part of it. Those composing so-called renal rickets, though not invariable, are usually obvious and often provide the features which bring the patients under medical observation. Though prominent they are not distinctive enough to secure agreement as to their causation and vary in different cases both in their radiographic and in their post-mortem appearances.

Thus L. G. Parsons[1] recognizes three forms radiographically:—(1) an atrophic form, which is practically identical with that seen in moderately severe cœliac rickets; (2) a florid form resembling that of infantile rickets, which he regards as possibly an earlier stage of the atrophic form; and (3) a woolly, stippled or honeycomb form, which is the most characteristic finding and quite unlike that of infantile rickets. In the last form there is osteoporosis of the shafts, an appearance of subperiosteal erosion and, in severe examples, a thickening and stippling of the bones of the cranial vault indistinguishable radiographically from that seen in Paget's disease. Despite this lack of resemblance Parsons states that he has no doubt that the changes are actually rachitic in nature, and thus agrees with Shipley et alii[2], who hold the same opinion, though admitting the differences in histology. Teall[3] also recognizes radiographically a variety like that of ordinary rickets, and a second corresponding to Parsons' third form. He regards the sub-periosteal eaten-away appearance as the most important diagnostic sign by X-ray examination.

In contradistinction to the views of Parsons and of Shipley and his co-workers, Brockman[4] emphasizes the distinction between renal and ordinary rickets. In the examination of three fatal cases he found that the shafts were straight and not curved as in infantile rickets, and ascribed the deformities to separation and displacement of the epiphyses, the solution of continuity and deformity being progressive. The most important distinction histologically was an active absorption of bone by osteoclasts in the region of the growth disc and of the shaft beneath the periosteum, and its replacement by fibrous tissue, exceeding the amount found in rickets. On the other hand Hunter[5] states that Professor Turnbull has found in a case of renal rickets which he examined the histological sections of the bones in all respects characteristic of rickets.

A consideration of these divergent findings, both radiographical and histological, leads one to the conclusion that in some cases renal rickets and infantile rickets are similar, but that in others some additional factor produces the special radiographic picture of the woolly, stippled or honeycomb form with osteoporosis and erosion, and the histological changes

described by Brockman. The case described below suggests that this factor is an excessive activity of the parathyroid glands in an endeavour to maintain the level of the calcium content in the blood, which is known in renal rickets often to be low and even to fall sufficiently to cause tetany.

The present case was a frank example of renal dwarfism with renal rickets, characteristically ending by uræmia, in which after death hyperplastic parathyroid masses were discovered accompanied by osseous changes, compatible with those of ordinary rickets and osteitis fibrosa in combination. The intervention of the parathyroid was suggested by Swart[6] after his study of a case of renal rickets (1930), but no autopsy was permitted.

Case report.

We now give the clinical, radiographic, post-mortem and histological reports on our case.

Clinical report.—The boy, aged 14 years, first came under observation in September, 1925, as a typical example of renal infantilism presenting at that stage no bony changes recognizable clinically or by X-ray examination. His appearance and stature resembled that of a boy of 9 or 10, rather than of 14, and the change in his health and failure to grow were dated by his mother from an attack of diphtheria at the age of 5. He passed up to 154 oz. of urine daily, of specific gravity 1004, containing a trace of albumin, but no casts. Polydipsia was a prominent symptom. The cardiac dullness was slightly increased, the aortic second sound accentuated, and the brachial arteries appeared to be slightly hardened. The blood pressure was: systolic 126 mm., diastolic 98 mm. Renal efficiency tests indicated gross defect in renal function, maximum and minimum concentration as estimated by Calvert's test each equalled 0·9 per cent., and the blood urea was 132 mgrm. per 100 c.cm. Before his discharge one month later the figures were little better, maximum concentration being 0·93 per cent., minimum 0·80 per cent., and blood urea 118 mgrm. per 100 c.cm. The Wassermann test was negative and no changes were found in the ocular fundi. There were no uræmic symptons.

He did not appear again until July, 1931, 6 years later, when aged 20 years. Despite the previous renal efficiency estimations he stated that he had felt perfectly fit until 6 months previously, and had been working on the stage doing odd jobs that came his way in connection with a touring company. For about 6 months he had noticed that he became tired on walking, and on examining his legs had found himself to be knock-kneed. This deformity increased rapidly and on consulting his doctor he was sent back to hospital, still protesting that he was in good health. On questioning him it was elicited that the polyuria and polydipsia had persisted, and that he had suffered from occasional headaches and attacks of epistaxis.

His height at 20 years was 4 ft. 6 in. and weight 18 kgrm., his complexion sallow, and nutrition poor; and there was now evident renal rickets, particularly at the knees, with pronounced genu valgum especially on the right side. He could walk only by the aid of a stick. The blood pressure was 119 mm. systolic, 78 mm. diastolic, and the brachial and axillary arteries were now distinctly thickened. There was slight hypertrophy of the left ventricle, the apex-beat being in the 6th space, half an inch outside the mid-clavicular line, and the impulse forcible. The aortic second sound was accentuated. The polyuria had led to definite distension of the bladder, producing a vesical dullness reaching to the umbilicus, which did not disappear on micturition. The urine still contained a trace of albumin and there were a few hyaline casts. The blood urea was 128 mgrm. per 100 c.cm., maximum and minimum urea concentration were each 0·5 per cent. By Volhard's test, 33 oz. of urine were excreted in 7 hours, and the specific gravity fluctuated between 1005

and 1008. He took his discharge and it is regrettable that no blood chemistry estimations are available.

Ten days later he was readmitted for epistaxis and soon developed uræmia which proved fatal. The urine contained 0·3 per cent. of protein and the blood-urea amounted to 355 mgrm. per 100 c.cm.

Radiographic report.—Figures 1 to 5 are from the case described, and show the woolly type of change seen in renal rickets. Figures 6 and 7 show a frankly rachitic type from another case, which is mentioned below and is included for the purposes of contrasting the one with the other.

FIG. 1.—Antero-posterior view of the left knee showing the coarse stippled type of osteoporosis, the subperiosteal erosion and the woolly changes at the metaphysis of the lower end of the femur.

The radiographs show both knees, and are the only skiagrams available except for one of the calvarium, which is of the post-mortem specimen.

KNEES.—The bones are small for the age, 20 years, and show marked osteoporosis, which is obvious even in the absence of a radiograph of the normal for comparison. The diaphysis shows a coarse stippling, or honeycomb appearance, and the cortex

is thinned to a line or series of lines. The epiphysis is ununited, but the most marked changes are to be seen at the metaphysis, and in this case, at the lower ends of the femora. In this region there is erosion of bone beneath the periosteum, making the end of the shaft too small for the epiphysis, and a woolly appearance from which all bone texture is absent; also the metaphyseal aspect of the epiphysis

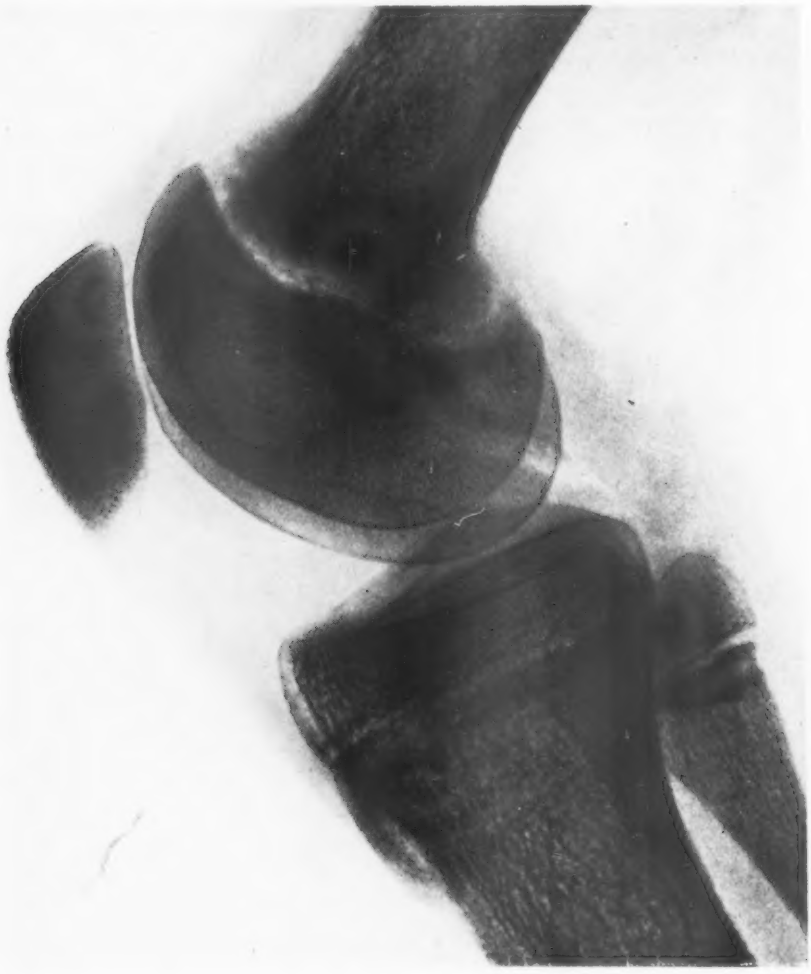


FIG. 2.—The lateral view of the left knee. There are no definite changes at the epiphysis of the upper end of the tibia or the fibula except the wide epiphyseal line.

appears to be slightly more hollowed than the normal. The shafts of the bones are straight, but the right knee shows a deformity at the lower end of the femur, which may be described as a slipped epiphysis. This, of course, may occur; but the typical change is one of progressive displacement and deformity, due to continuous erosion of bone at the metaphysis. The changes tend to be asymmetrical and may be much more marked in one region than another, but the presence of a deformity possibly makes the condition appear less symmetrical than it really is.

CALVARIUM.—This radiograph was taken of the specimen in a direction which is not possible in the living subject, and so presents an aspect not commonly seen with consequent difficulties in interpretation.

Osteoporosis, however, is definite and there is very marked coarse stippling, both the outer and inner tables being ill-defined, and no definite diplöe can be made out at the borders. There are five round transradiant areas more or less close to the sagittal suture, but it will be noticed that three of these, the most circular and precisely defined, receive the terminations of undoubted vascular markings; the other two are much more like pathological changes in the bone.

FIG. 3.—Antero-posterior view of the right knee. The changes are more extensive, the erosion is more marked on the inner side and there is a genu valgum deformity.

The changes in the skull may be such as to resemble closely those seen in osteitis fibrosa and Paget's disease. Generalized osteoporosis is present in the frankly rachitic type, but it does not present the same coarse stippled appearance, and it is interesting to note in this connection, that a coarse stippling very like, if not identical with, this is described by Camp and Ochsner[7] in their radiological study of the bone changes in hyper-parathyroidism associated with parathyroid tumour. They described it as of a miliary granular appearance, and state ' that it is best observed in the skull, and that it appears to be peculiar to hyper-parathyroidism.'

CONTROL CASE.—Figures 6 and 7 are from another case of renal rickets, aged 17 years, and show the appearances seen in the frankly rachitic type. The appearances at the epiphysis are those of infantile rickets on a grand scale. The shaft is splayed out at the epiphysis into the typical champagne glass deformity, the edges beneath the periosteum are serrated and sharply defined, the epiphyseal gap is much wider than that in the woolly type, and the diaphysis appears too big for the size of the epiphysis. The changes are more symmetrical and curvature of the long bones may develop.

FIG. 4.—Lateral view of the right knee. There are slight but quite definite changes at the upper end of the tibia. The arrow indicates an area which is suggestive of callus.

In the woolly type, the X-ray appearances alone may be considered as pathognomonic of the condition, but a full dossier will be necessary to differentiate the rachitic type from cœliac, recurrent and late rickets. The marked difference in radiographic appearances suggests a different ætiology, or the presence of some modifying factor.

Post-mortem examination (Sept., 1931, P. M. 215/31).—The general development approximated to that of a boy of 10 years; hair was present, however, on the upper lip and pubes. Body weight 18 kgrm., body length 128 cm. Bilateral genu valgum, more marked on right side.

Heart (170 grm.) of typical renal type, with considerable hypertrophy of the ventricle; general hypertrophy of the arteries without atheroma. Slight hypostatic pneumonia at base of left lung. Slight mucous catarrh of stomach; intestines normal, long retro-cæcal appendix extending up to hepatic flexure of colon; parenchymatous degeneration and œdema of liver; gall bladder, bile ducts, and pancreas normal. Spleen normal in size, pale, Malpighian bodies small. Thymus rather œdematous, and persistently glandular. Thyroid normal size, pale, with excess colloid. Adrenals large, with much lipoid in the cortex. Pituitary very small, the apparent separation between the lobes being very near the anterior pole (see histology); rounded swelling (0·8 × 0·6 × 0·8 cm.) at the attachment of the infundibulum to the floor of the third ventricle. Pineal gland possibly slightly enlarged. Brain otherwise normal.

Parathyroids.—Four enlarged parathyroids were found, the largest two (1·0×0·7×0·45 cm. and 1·5×0·8×0·4 cm.) being in relation to the lower pole of the left lobe of the thyroid, the other two being at the lower pole of the right lobe. All were encapsulated oval bodies with a definitely brownish colour. From the same region were removed diffuse masses resembling fatty tissue, but sinking in water.

Kidneys.—Both kidneys were very small (total weight 100 grm., sizes 8 × 3·2 × 1·7 cm. and 6·6 × 3·3 × 2 cm.), and typically granular in appearance. The subcapsular surface showed uniformily distributed pale yellow regeneration nodules, alternating with pinkish-grey depressed zones adherent to the capsule. The demarcation between cortex and medulla was poorly marked, the cortex thinned out irregularly and showed a poor pattern with occasional cysts. The arcuate vessels showed hypertrophy but no occlusion of their lumina. Bladder hypertrophied, ureters dilated, prostate and urethra normal. Testes small and resembled infantile type.

Bones.—All the bones were much softer than normal, and it was possible to cut chips off the calvarium and vertebræ with a knife. The costo-chondral junctions were enlarged, and on cross-section showed a ragged widened and congested zone at the line separating bone and cartilage. The lower epiphysis of the right femur was twisted laterally so that the articular surface faced outwards, and the inner condyle consequently appeared to be enlarged. All the epiphyseal cartilages were thickened (lower end 0·7 cm., great trochanter/shaft 0·2 cm., head/shaft 0·6 cm.) and irregular; and broad hæmorrhagic zones were present in them, especially in that at the lower end of the shaft, where there was an almost complete transverse division of the cartilage by hæmorrhage. In this hæmorrhagic zone were gritty calcified areas. The cortex of the shaft was thinned, especially at the two ends, and the marrow was fatty in the lowest quarter and the dull brown-red in the remainder of the shaft.

Histological examination. Bones.—Portions were taken from the parietal bone, the costo-chondral junctions, and the shaft and lower end of the femur, and rapidly decalcified in Jenkin's fluid. Similar material was left in Muller's fluid for six months, followed by brief treatment with Jenkin's fluid before embedding, to study the distribution of calcification. Sections were also cut from a costo-chondral junction without any preliminary decalcification to confirm the picture afforded by the Muller sections.

Parietal bone.—All the bony lamellæ are thinned out as the result of lacunar resorption, and on the surface of each is a layer of osteoid tissue, only the central part being calcified. Osteoclasts are present in large number in the lacunæ and in other parts of the marrow spaces. The marrow otherwise consists of fine collagenous fibrils and histiocytes, there being no hæmopoietic elements (Fig. 8).

FIG. 5.—Calvarium, showing the coarse stippled or miliary granular appearance, and the five transradiant areas.

Costo-chondral junctions.—The bone-cartilage junction is irregular, and in places there are peninsular processes of cartilage almost cut off from the main mass of cartilage. There is an abnormally wide zone of proliferating cartilage, consisting of irregularly arranged groups of large swollen cells with little matrix. Provisional calcification is poorly marked, being present only in immediate contact with the line

FIG. 6.

FIG. 7.

FIG. 6 and 7: A control case of renal rickets, aged 17 years, showing the frankly rachitic type of change with a wide epiphyseal gap and the champagne-glass appearance at the metaphysis.

of ossification, and even there it is deficient, the line of calcification being broken. Against provisionally calcified cartilage bone is forming in the usual way with a thin intervening line of osteoid tissue (possibly in slightly excessive amount), but apart from these small islands of true bone the first two millimetres from the

cartilage is represented by fibrous marrow, numerous large active osteoclasts, and coarsely fibred osteoid tissue. The character of the tissues then changes in a rather definite oblique line, and suggests the possibility of these appearances being determined in some degree by a previous fracture. The bone thereafter is lamellar, but the lamellæ are small with numerous lacunæ, and nearly all are covered with a layer of osteoid tissue. The marrow is patchy, partly hæmopoietic and partly finely fibrillar collagen, occasionally fatty, but everywhere contains numerous large active-looking osteoclasts.

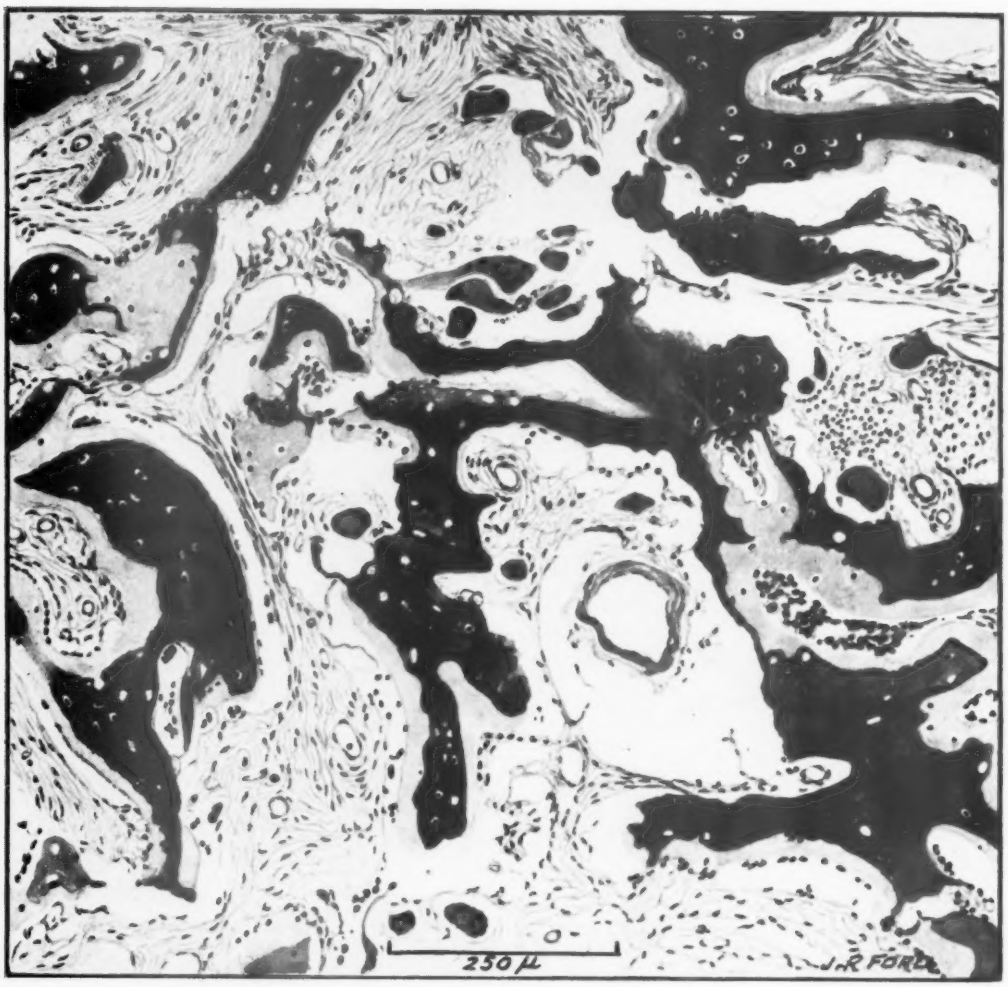


FIG. 8.—Transverse section of parietal bone : showing lacunar resorption of bone by osteoclasts, and the fibrous marrow : except where resorption is taking place, the bony lamellæ are covered with a layer of osteoid tissue.

Lower end of femur.—The epiphyseal cartilage is fractured along the hæmorrhagic line which traverses it, so that it presents four surfaces, metaphyseal, epiphyseal, and one on either side of the fracture. Proliferation is taking place in relation to all of these, with the result that there is no resting cartilage. Provisional calcification is greatest on the epiphyseal surface, where it forms an almost unbroken line; on the metaphyseal surface calcification is patchy as in the ribs; there are a few calcified foci on each fracture surface. The fracture space is filled with red blood corpuscles, with

numerous proliferating blood vessels; at the edges are collagenous fibrils and histiocytes; and in the centre scattered patches of coarsely fibred osteoid tissue (with slight calcification of the larger masses), the whole resembling callus. The epiphysis shows lamellar bone in small amount next the cartilage, each lamella being surrounded by a thin layer of osteoid tissue. Further back from the cartilage the lamellæ are well formed, and very little osteoid tissue is seen. All the marrow is fatty, and otherwise practically non-cellular. On the metaphyseal side, small lamellæ of bone are related to the calcified parts of the cartilage. Each is covered with a thick layer of osteoid tissue and surrounded by a single row of osteoblasts. Between them is fibro-cellular marrow containing islands of osteoclasts. Further up the bone and in the shaft there is not so much osteoid tissue, but quite a definite layer can still be seen covering each lamella of bone. The marrow is variable in appearance, in places fibrous, in other places fatty with occasional hæmopoietic foci. Where the marrow is fibrous, it is always associated with numerous osteoclasts and lacunar resorption of bone (Fig. 9).

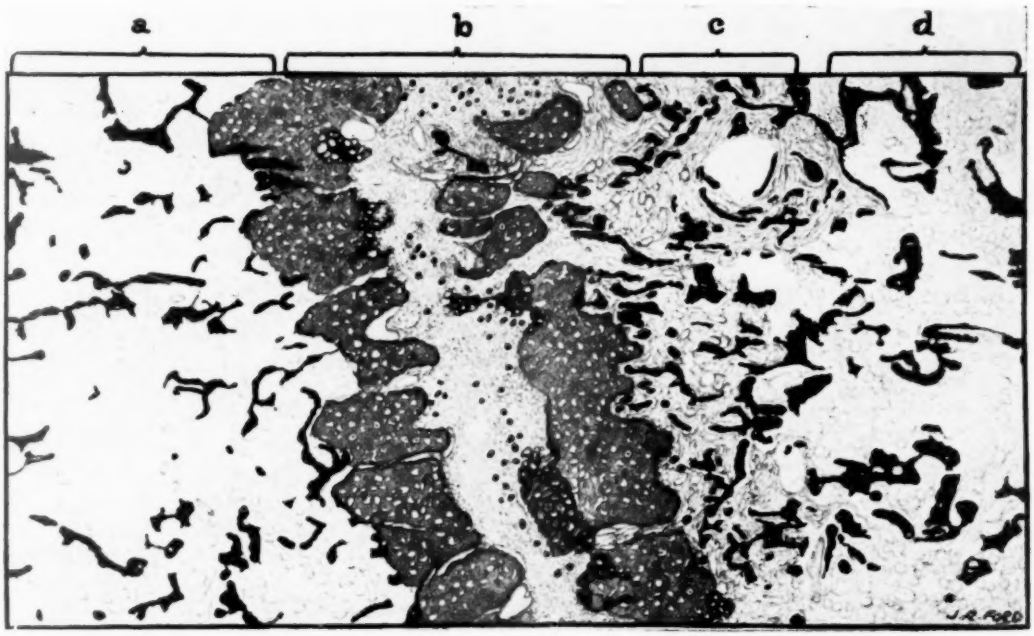


FIG. 9.—Longitudinal section through epiphyseal cartilage of lower end of femur.
a = epiphysis. *b* = epiphyseal cartilage with hæmorrhage, coarse fibred bone, osteoclasts, etc., occupying the fracture which traverses it. *c* = metaphysis with fibrous marrow and osteoclasts. *d* = diaphysis.

KIDNEY.—The glomeruli show hyaline changes, adhesions, necroses, and in many cases complete fibrosis. All the glomeruli seen are affected. No proliferation of Bowman's epithelium is seen. Many of the glomeruli are greatly enlarged, while others are shrunken. Degenerative changes are present in the tubular epithelium. There are numerous large regeneration nodules. The interstitial tissue is the seat of much reticular fibrosis in the form of thick bands of collagen with numerous areas of lymphocytic infiltration. The vessels show hypertrophy with reduplication of their internal elastic laminæ. The histological picture appears to conform to the type described by Russell[8] as characteristic of renal dwarfism, i.e., nephritis repens, type 3.

PARATHYROIDS.—The large encapsulated mass from the left side consists of parathyroid tissue, not dissimilar to the tumour-like nodules described recently in numerous cases of osteitis fibrosa. It consists of small polygonal cells arranged in

rounded acini, and intersected in places by bands of fibrous tissue. Very few oxyntic cells are present. It probably represents a functional hyperplasia of the gland. The encapsulated masses from the right side are similar, but conform more closely in appearance to the normal parathyroid. The diffuse masses of tissue removed from the retro-thyroid region consist of œdematous fat, fibrous tissue, and lymph glands showing hyperplasia of the sinus endothelium.

PITUITARY.—The whole of the bi-lobed structure occupying the sella turcica is composed of anterior lobe tissue, the anterior section consisting mainly of chromophil cells of both types, and the posterior of chromophobe elements. The posterior lobe of the pituitary is represented by the nodule at the base of the infundibulum, which consists of tissue resembling the pars nervosa, covered with a thin layer of pars intermedia tissue.

OTHER ORGANS.—Pineal gland somewhat enlarged, but structure normal. The suprarenals are large, with much lipoid in the cells of the outer part of the cortex, medullary cells large with darkly staining nuclei. The thymus, is œdematous, showing a proportion of glandular to adipose tissue normal for age; also very large Hassal's corpuscles, consisting mainly of keratin and cell debris. The thyroid vesicles are large and full of colloid, with epithelium flattened. The pancreas shows numerous well formed islets of Langerhans. In the tests spermatogenesis is not well marked, only in a few tubules. There are very few interstitial cells. The prostrate is normal; the unstriated muscle of the gland fuses with voluntary muscle fibres running in from outside. The bladder shows hypertrophy. The lungs, liver, and spleen are normal. The myocardium (left ventricle), aorta, and femoral artery show typical hypertrophy.

Discussion.

Bone histology.—The bone changes in renal infantilism are inconstant. In many cases, as is well known, there are no skeletal abnormalities at all except the general osseous under-development proportionate to the size and stature of the subject. In a second group of cases, deformities and bony changes occur, and as mentioned above, Hunter[3] reports that Turnbull has demonstrated the bony changes of true rickets in such cases. The present case, which has many histological points of resemblance to that recorded by Brockman[4], cannot be so classified, as although some of the appearances are strongly reminiscent of rickets, other changes are present which are not typical of the latter condition. Of these, the chief are the great osteoclastic activity and lacunar resorption of the bony lamellæ. In sections of true rickets which have been compared with the present sections, osteoclasts are present in appreciable number only in the subperiosteal part of the bone. Osteoid tissue is found in both conditions, but in much greater amount in true rickets. In rickets, the marrow displays more hæmopoiesis, but this may be due to the difference in age. Provisional calcification of the cartilages is limited in the present case to the immediate neighbourhood of the epiphyseal line, whereas in the case of rickets calcified foci are also found some little way back from it; the total amount of provisional calcification is, however, about equal in the two conditions. Fractures of the epiphyseal cartilages were not seen in the true rickets sections.

The lacunar resorption of bone, large number of osteoclasts, and fibrous marrow of the shafts of the long bones and skull bones conform very closely to the appearances in osteitis fibrosa, and in this connection interest attaches

to the multiple endocrine changes, in particular the hyperplastic parathyroid bodies. The bony changes as a whole may be regarded as a composite picture of osteitis fibrosa and true rickets.

Parathyroid factor.—It is recognized that parathyroid hyperplasia, with or without adenomata, is closely associated with gross osseous defects, in some of which it is generally regarded as preceding the bony changes whilst in others it is secondary. The surest example of parathyroid over-functioning as the cause of bone disease is generalized osteitis fibrosa for, as Hunter[9] points out, in this disease hypertrophy or tumour formation is almost always confined to one parathyroid, the others remaining normal. However, it must be remembered that Erdheim[10], who described three cases of parathyroid enlargement in association with osteomalacia, held the view that the skeletal changes precede those of the parathyroid; and Hoffheintz[11] who collected 45 cases of measurable enlargement of one or more parathyroids, in 27 of which there was definite bone disease, found that whilst 17 were of generalized osteitis fibrosa, there were 8 of osteomalacia and 2 of rickets. Parathyroid hyperplasia has also been met in connection with experimental rickets in rats, in association with want of sunlight, with a deficiency of calcium ingestion and even with carcinomatous infiltration in bone[12], and in multiple myelomata[13]. Pappenheimer and Minor[14] have described parathyroid hyperplasia in rickets in children, and Linder and Vadas[15] record a case of its association with late rickets in a boy of 15 years.

Despite the satisfactory results obtained by removal of the parathyroid tumours in generalized osteitis fibrosa, Barr and Bulger[16] hold that there is a case for regarding the bone changes as primary even in that disease. Hilding Bergstrand[17] believes that the histological changes in the bones in cases of generalized osteitis fibrosa are not peculiar, and that a similar picture occurs in physiological lacunar resorption and in many other various pathological conditions. He exemplifies this by illustrations of pathologically increased bone resorption in cases of ' chronic glomerulo-nephritis ' with or without parathyroid enlargements, and describes a case in which the bony changes were slight but there were two hyperplastic parathyroid swellings, each the size of a plum, in a patient in whom chronic nephritis was also present.

Another example of parathyroid enlargement in association with renal disease is recorded by Harbitz[18] in which adenoma of a parathyroid gland accompanied ' chronic interstitial nephritis.' The patient had brittle osteoporotic bones containing many smooth-walled cysts. The bones were soft, readily fractured, and could be cut easily. MacCallum[19] describes a case where parathyroid adenoma occurred in a young man who died from uræmia due to ' chronic interstitial nephritis,' but in which no mention is made of bony changes.

A study of the literature would suggest that while parathyroid hyperplasia and adenomata are probably primary in true cases of generalized

osteitis fibrosa, they may occur as secondary developments in other diseases of bone and in various other states including rickets and chronic nephritis. It appears, therefore, that the discovery of parathyroid hyperplasia in our case of renal rickets together with osteoclastic resorption in the bones, is no mere fortuitous finding, but must be considered to be a part of the picture of the malady. The unusual length of time which the boy lived, more than six years after his renal inefficiency had become serious enough to produce a blood-urea value of 132 mgrm. per cent., may explain the existence of parathyroid masses large enough to be obvious.

We suggest as an explanation of the bony changes that although the chronic renal disease occurring in renal dwarfism may cause true rachitic changes in the bones, yet that the most characteristic osseous changes seen radiographically as the honeycomb, stippled or woolly form, are due to osteoclastic resorption, the result of secondary parathyroid overactivity.

We wish to thank Dr. H. Courtney Gage for the radiograms and for his radiological report.

REFERENCES.

1. Parsons, L. G., *Dis. of Children*, Garrod, A. E., *et al.*, Lond., 1929, 2nd Ed., 122.
2. Shipley, P. G., *et al.*, *Am. J. Dis. Child.*, Chicago, 1922, XXIII, 91.
3. Teall, C. G., *Brit. J. Radiol.*, Lond., 1928, N.S., I, 19.
4. Brockman, E. P., *Brit. J. Surg.*, Bristol, 1927, XIV, 634.
5. Hunter, D., *Lancet*, Lond., 1930, i, 1004.
6. Swart, H. A., *J. Bone & Joint Surg.*, Boston, 1930, XII, 876.
7. Camp, J. D., & Ochsner, H. C., *Radiology*, St. Paul, 1931, XVII, 63.
8. Russell, D. S., *Med. Res. Council Sp. Rep. Ser.*, 1929, No. 142, 149.
9. Hunter, D., *Lancet*, Lond., 1930, i, 950.
10. Erdheim, J., *Sitzungsber. d. Kais. Akad. d. Wiss.*, Vienna, 1907, 3 Ab., CXVI, 311.
11. Hoffheinz, *Virchows Arch. f. path. Anat. u. Physiol.*, Berlin, 1925, CCLVI, 705.
12. Klemperer, P., *Surg. Gyn. & Obst.*, Chicago, 1923, XXXVI, 11.
13. Barr, D. P., & Bulger, H. A., *Am. J. Med. Sci.*, Phil., 1930, CLXXIX, 447.
14. Minor, J., & Pappenheimer, A. M., *Proc. N.Y. Path. Soc.*, N.Y., 1921, N.S., XXI, 98.
15. Linder, G. C., & Vadas, D. G. M., *Lancet*, Lond., 1931, ii, 1124.
16. Barr, D. P., & Bulger, H. A., *Loc. cit.*
17. Bergstrand, H., *Act. Med. Scandinav.*, Stockholm, 1931, LXXVI, 128.
18. Harbitz, F., *J. Med. Res.*, Lond., 1915, XXXII, 361.
19. MacCallum, W. G., *Bull. Johns Hopkins Hosp.*, Baltimore, 1905, XVI, 85.

ON THE OCCURRENCE OF SEX-LINKED VARIATIONS IN TWINS

BY

C. E. KELLETT, M.D., M.R.C.P.
(From the Babies' Hospital, Newcastle-on-Tyne.)

During the past few years it has become apparent that disease is by no means the necessary response of an organism to infection, and further, that the type of disease produced depends not only on the nature of the infecting agent but also on the state of the organism infected. So has room been found for considerable speculation, much of which could be confirmed, or disposed of, were it adequately controlled.

Such a control of the soil factor, as opposed to that of the seed, would apparently be adequately provided for, if the disease processes were studied in a number of identical twins, as suggested by Galton[1]. Despite his advocacy and the papers published in 1911 by Cockayne[2] and in 1925 by Murray[3], this method of approach, laborious yet of considerable promise, has been comparatively neglected in this country. In Germany particularly, during the past few years, has an attempt been made to acquire insight by this means. Not only has a mass of somewhat heterogeneous information been collected on the response of twins to the more common infectious diseases and analyzed in papers such as those of Glatzel[4], but the problem has been rather more widely reviewed by Stransky[5], Curtius[6], Siemens[7], and von Verschuer[8], as well as by Francioni[9] in Italy, and Apert[10], and more recently Pommert[11], in France.

This method of approach has been applied by Siemens[12] to the study of skin conditions, by Korkhaus[13], Siemens and Hunold[14] to those of the mouth and teeth, and has in particular yielded information on the constitutional factors involved in the development of tuberculous infection, of insanity and crime, through the work more especially of Diehl and von Verschuer[15] and of Lange[16]. As a deliberate control identical twins were employed in a feeding experiment by Bernheim Karrer[17].

TABLE 1.

SEX INCIDENCE OF TWINS.

	Male pairs.	Female pairs.	Mixed pairs.
German Empire (1906-1911)	49,425	46,637	58,382
United States (1921)	6,639	6,484	6,898
Nichols data (Newman[18])	234,497	264,098	219,312

The justification for all such work, admittedly tedious and painstaking, resides in the belief that so-called identical twins are monozygotic and have arisen from a single ovum fertilized by a single spermatozoon. Such twins must of necessity be of the same sex, and since the laws of chance demand that there should be as many like-sexed dizygotic twins as there are of unlike sex, the discrepancy between the actual incidence as shown in Table 1 and the theoretical ratio of 1:2:1 constitutes a statistical proof in favour of the existence of such twins. The only satisfactory explanation of this discrepancy is, as Newman[18] points out, the assumption that nearly half the like sexed twins are monozygotic, ' and hence morphologically stand for but one individual to a pair.' From these figures Weinberg[19], and many after him, have arrived at an estimate for the relative incidence of such identical twins, which Bonnevie and Sverdrup[20] have shown to be in reasonable agreement with those arrived at from a clinical study of the fœtal membranes. About 21 per cent. then, only, of all twins born are probably identical twins. It should, however, be noted that direct evidence of monozygotic twinning in man was not forthcoming until 1922, when Arey[21] described a specimen of twin embryos in which he could actually demonstrate their origin from a ' single yolk sac and hence from a single ovum.'

The incidence of multiple births has recently been studied by Greulich[22] in a series of 21 different countries. The percentage of multiple births was found to vary remarkably for different countries, ranging from 1·59 twin births in Denmark to 0·40 in Colombia. On the average, as is generally received, he found that there is one set of twins for each 85 confinements, while the ratio of other multiple births—triplets 1 to $85 \cdot 3^2$, quadruplets 1 to $87 \cdot 3^3$—is in close agreement with those demanded by Zeleny's[23] hypothesis.

The variation which may occur within a community, from which emerges the hereditary nature of twinning, has perhaps most clearly been shown by Bonnevie and Sverdrup[20] who have taken advantage of the relative geographical isolation of such communities as those in the valley of the River Orkla, in Norway. While the average percentage of twin-births in the Norwegian population proved to be 1·46, their twin families gave 3·25 and in special twin-lines the percentage was raised even to 8·23.

Neither they, nor Davenport[24], nor indeed any one else, has shown how this tendency is transmitted. This in part would seem to be due to the possibility that a different hereditary mechanism may be at play in the case of dizygotic as opposed to monozygotic twins. That this is the case is strongly suggested by the different relations that exist between the age of the mother and the percentage of monozygotic and dizygotic births. As first shown by Weinberg[19], there is an increase in the frequency of dizygotic twin births until the age of forty, but little or no change in the frequency of monozygotic twin births.

Not only are twins relatively rare, but like-sexed twins require careful examination before it can be determined whether or not they are identical twins. Since such a determination must depend in the main upon the

establishment of certain deep-seated resemblances; in this case our very reason for studying monozygotic twins, the necessity for certain rigid and accepted standards is apparent.

The elaboration of such standards is by no means easy, for even when such information is available, the existence of multiple or single chorions cannot be said to constitute unimpeachable evidence. Curtius[25], in a recent study of twins whose birth history had apparently been accurately recorded, found 7 pairs out of a total of 19 like-sexed pairs that were identical. Of these seven, three pairs were mono-chorial, 3 di-chorial, and 1, because of the poor condition of the fœtal membrances, had been recorded as being doubtful. Again, von Verschuer[26] has recently described an example of mono-chorionic though apparently dizygotic twins. It is as a result of such findings, that, as Newman[27] suggests, ' such careful and capable students of human twins as Siemens, v. Verschuer, and Dahlberg have been forced to rely exclusively upon the similarity method of diagnosis and to give only very secondary consideration to fœtal membranes '; and, indeed, such an attitude implies no more than a recognition of the possibility that the twinning division may take place prior to the trophoblast stage, a possibility that may apply not only to twinning but also to other multiple births, for Komai and Fukuoko[28] describe what they believe to be a set of dichorionic identical triplets.

The similarity method of diagnosis has been elaborated in the main by Wilder[29], Thorndike[30], Danforth[31], Bonnevie[32], Cummins[33], Newman[34], Dahlberg[35], Stocks[36], and Lauterbach[37]. A considerable amount of data dealing with hand and foot prints, measurements, left-handedness, mirror reversal, and so on has been collected; and Fisher[38], moreover, has submitted Thorndike's and Lauterbach's results to statistical examination. Nevertheless, though it is conceivable that, as Newman maintains, by this means even the most refractory case may be resolved, there is not only an obvious danger in such a method of approach—Hogben[39], for instance, quotes Stocks[36] as having ' rightly remarked that " in no branch of scientific investigation is the circular method of reasoning so common " '—but also a very marked subjective element is, as Stocks has demonstrated, still present, so that as he says ' it is therefore surprising to find with what assurance many writers on the question of twins regard their own ability to diagnose the monozygotic from the dizygotic with certainty, which can only be explained by the fact that no satisfactory check has so far been devised as to whether the diagnosis was right or wrong.'

My purpose in this paper is to call attention to a certain small group of like-sexed twins in which for other and more fundamental reasons their nature is known, and which therefore would appear to constitute just such a check.

In man, as well as in many animals, a number of genes appear to be located in the sex chromosome, and are linked with sex in a curious and clear cut way. The female somatic cells have each two chromosomes (XX), one from each parental germ cell, while the male has only one X chromosome

and this is derived from the egg. It is associated with the so-called Y-chromosome which carries few active genes. Now in the female an affected chromosome X will as a rule be balanced by the second X-chromosome, but in the male such a balance will not be achieved, and may become manifest as a sex-linked malady, such as those recently reviewed by Davenport[10]. ' Thus the chromosomes offer a complete explanation of a very complicated form of hereditary behaviour ' (Gates[11]).

It would seem impossible for only one of like-sexed monozygotic twins to be affected with such a hereditary condition; that, however alike such twins may be, as were for instance those described by Nettleship[12], they must be dizygotic.

Examples of sex-linked conditions occurring in twins are of a necessity somewhat rare, and with the exception of the tantalizingly incomplete descriptions given by Nettleship of two lots of apparently identical twins in which only one of each was affected with colour blindness, in pedigrees where they have occurred little information has been given concerning them. Fischer[43], Gould[44], and v. Manteuffel[45] have recorded pedigrees of hæmophilia in which both twins were affected, and Sadler[16] and de Lacy[17] in which only one of the like-sex twins was affected. Ash[18] has recorded briefly a pedigree of sex-linked microphthalmia in which only one of like-sexed twins was affected, and further instances of colour blindness in twins have recently been summarized by Waardenburg[19].

The following case of clearly defined sex-linked hereditary nystagmus occurred in only one of like-sexed twins, who are therefore, it is suggested, of dizygotic origin. It is reported in detail in the belief that an accumulation of such records will ultimately serve to discredit or else confirm the present methods of distinguishing between the two types of twins.

On the present assumption that monozygotic twins resemble one another more closely than do dizygotic twins, the value of known dizygotic twins as checks varies directly as the degree in which they resemble one another.

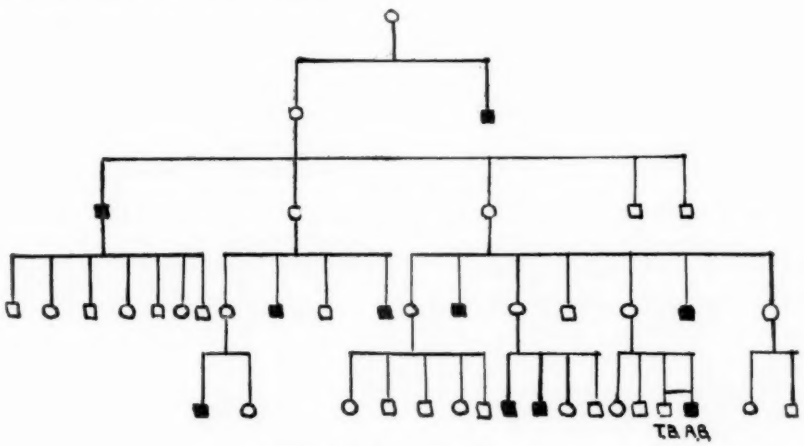
It is interesting therefore to note at this point, the paradoxical dissimilarity that has been noticed by Reichle[50] and others to occur in conjoined twins; for these as Newman[51] maintains, constitute in all probability the only group of twins ' that are indubitably monozygotic.' This dissimilarity is probably adequately explained by him on the assumption that it is no more than the inevitable expression of the twinning division having occurred relatively late in their development, when the two halves of the embryo will no longer be equipotent but one half will have right-handed tendencies and the other left-handed. It follows from this that the earlier twinning division takes place the more alike identical or monozygotic twins will tend to be, and this may explain why in certain series the most obviously monozygotic twins have been di-chorionic.

On January 20th, 1933, A. B., aged 2¼ years, was brought to the Babies' Hospital by his mother because of his failure to put on weight, and his recurrent attacks of fever and cough. During the past 4 months, the child had had 3 such attacks. The first one lasted for about a fortnight and was associated with a fever, his

temperature on the occasion it was taken being 102°. During this period he lost about 2 lb. in weight; at that same time his brother, though he appeared to be quite well, also lost about 1 lb. in weight. Since then neither of the twins had gained weight regularly, and A. B. had had two further attacks of fever, though in each case they were of rather shorter duration.

The health of the twin brother T. B., and of the only other child, a boy aged 5, had not in any way given the mother anxiety, and she was not concerned at the very marked and coarse lateral nystagmus that A. B. alone showed, since it was well known in her family that for generations certain of the male children had been so affected.

Her husband was one of twins, and twins had been known to occur in his family, but were reputed never to have occurred in hers. Both she and her husband were healthy, an aunt, however, whom the twins had frequently visited had died that Christmas of Addison's disease.



GRAPH I.—Pedigree of twins.

Graph I summarizes the pedigree of the twins. Their great great grandmother was born in Northern Ireland, and it is a tradition of the family that the nystagmus had been present in certain of the men of the family for many former generations. This nystagmus appears to have been invariably definite and clear cut, and to have been sex-linked.

Such pedigrees of sex-linked hereditary nystagmus are relatively rare, but examples have been published by Owen[51], Clarke[52], Caspar[53], Muller[54], Evans[55], Auden[56], Nettleship[57], Nodop[58], Cockayne[59], Englehaard[60], Waardenburg[61], Hemmes[62], and Holm[63]. The ætiology of this condition is obscure. Nettleship considered it to be often an expression of partial albinism, but as Cockayne points out such an explanation cannot apply to the family whose pedigree he gives, who are Italians, and darkly pigmented. Both A. B. and T. B. too have dark brown eyes, and showed on examination no gross deficiency in retinal pigmentation. In short, little is known of this condition, which is of interest here since it so sharply distinguishes one twin from the other.

It is therefore unfortunate that superficially the twins apart from their pigmentation do not very closely resemble one another. As their photographs show there are distinct differences in the shapes of their heads. Their response, however, to certain external factors appears to have been similar.

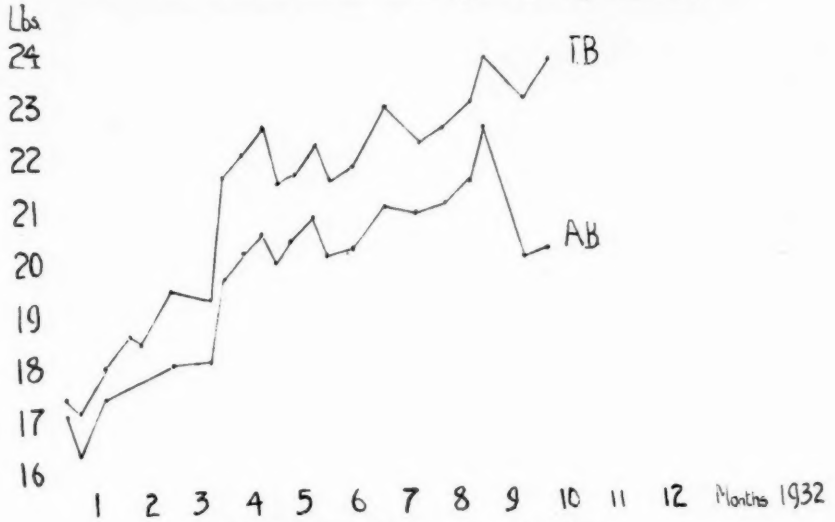
A. B.

T. B.

A. B.

T. B.

Though A. B. when first weighed was ½ lb. lighter than T. B. the variations that took place in their weight charts even during the last year, when A. B. was noticed to be ill, are, as shown in Graph II, very similar.



GRAPH II.—Weight curves of twins.

Both showed on being tested with tuberculin intra-dermally a markedly positive response, and presented on X-ray examination a very similar picture of increase in the peri-hilum shadows; and the discrepancy between their mode of response to this infection, for in the case of A. B. this relatively recent tuberculous infection was considered to be responsible for the bouts of unexplained fever, was to some extent dispelled by T. B. subsequently developing in the early part of February an apparently identical febrile attack.

Siemens[64] has stated that the probability of two twins with identical hair and eye colouring being dizygotic is remote; yet in these two boys the colouring of the hair, a rather peculiar ashen blond with a tawny glint, and of the eyes, which were a darkish brown like those of the father, and unlike the blue eyes of the mother and eldest boy, were identical. He insists, however, that in ' isolated cases ' this would not suffice for diagnosis, and gives a list of other traits in which monozygotic twins usually show strong resemblances to one another and dizygotic twins only rarely; a scheme which he points out can be extended as desired, through the inclusion of other traits and is therefore ' capable of unlimited development.' Such a scheme, which has also been adopted by Newman, and is generally approved, would appear to be one singularly susceptible of circular reasoning, and its appraised quality of unlimited extension quite peculiarly suspect. For it is clear that if twins are to be employed for the purpose of distinguishing between the operation of external and inborn factors, the briefer the scheme adopted in determining their identity, and the more it is dependent on simple anatomical factors, capable if possible of arithmetical expression, the better. Schemes of this general type, some of which have been recently reviewed by

Komai[65], while often comprehensive, are so vague and ill-defined that they scarcely admit of being checked by cases of the type that is being described, and indeed would not seem to offer the clinician much assistance in the classification and recording of the few isolated but significant cases of disease in twins which he is likely to encounter.

Stocks has endeavoured to fill this want. Facial resemblance and pigmentation are alike rejected by him as being variable and simply of ancillary value, and he believes that finger-print resemblances between corresponding fingers in twins furnishes the best means of separating monozygotic from dizygotic twins. ' This depends on the criterion that monozygotic twins have six or more patterns alike on corresponding fingers of the same-sided hands, whilst dizygotic have six or less alike; in the ambiguous case when six are alike the diagnosis is completed by comparing the differences in height and four simple head measurements with tabulated values.' His definition of alikeness is confessedly rather vague, and is that to a ' casual examination they should appear the same,' though this ' casual examination ' implies an examination that only just falls short of counting the ridges, and a very close resemblance.

Both the finger patterns and the palm patterns, that are inserted because of their documentary value, show differences that, in the case of the finger patterns at any rate, so far as his scheme is concerned, are significant.

Had it been necessary to go further it is clear from Stocks' table of limiting differences that the measurements of the twins are such as to reaffirm their dizygotic origin.

TABLE 3.

LIMITING DIFFERENCES FOR DIAGNOSIS OF LIKE-SEXED TWINS (STOCKS).

Age last birthday.		3	4	5	6	7	8	9	10	11	12	13	14
Height (cm.)	Boys	3·7	4·1	4·5	4·8	5·2	5·5	5·9	6·3	6·7	7·0	7·4	7·8
	Girls	3·0	3·6	4·1	4·7	5·2	5·7	6·3	6·9	7·4	8·0	8·5	9·1

Head length	5·5 mm.
Head breadth	4·5 mm.
Horizontal circumference	13 mm.
Interpupillary distance	3 mm.

TABLE 4.

MEASUREMENT OF TWINS.

	A. B.	T. B.
Height, standing	30″	$30\frac{1}{4}$″
Height, sitting	$17\frac{1}{2}$″	18″
Weight	20 lb. 11 oz.	23 lb. $4\frac{1}{2}$ oz.
Skull, length	154 mm.	165 mm.
Skull, breadth	130 mm.	145 mm.
Cephalic index	84	88
Horizontal circ.	$18\frac{1}{4}$″	$19\frac{3}{4}$″
Supra-auricular transverse circ. ...	12″	14″
Colour of eyes	Dark brown	Dark brown
Colour of hair	Very fair	Very fair
Whorl of head hair	Clock-wise	Clock-wise
Handedness	Right	Right

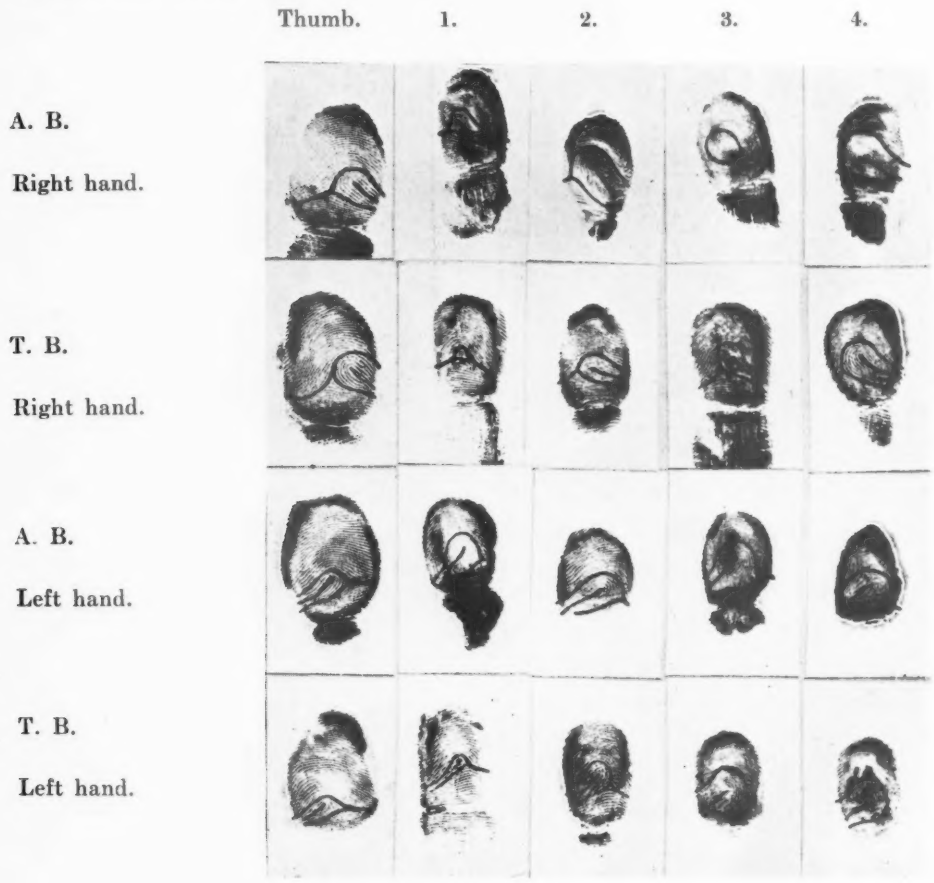
A. B., right hand.

T. B., right hand.

A. B., left hand.

T. B., left hand.

Lauterbach[37] has described two pairs of twins so alike that he would have classified them as being monozygotic were it not that in each case they were of unlike sex. It is probable then that the differences between these two children are greater than in theory they need have been, and to that extent their value as a check is impaired. As it is they have confirmed the method laid down by Stocks.



Until, however, such methods for classifying them are adequately checked, the degree of identity of twins, if they are to be employed in medicine as controls, should be determined by methods that admit of accurate definition and recording.

Summary.

A body of thought has during the past few years arisen that tends to emphasize once more the rôle played by the constitution of the infected organism in determining the type of disease pattern.

Just as it was found essential to subject the rôle played by the infective agent to control, so too an attempt should be made to control this second factor. Such a control would seem to be almost ideally provided were such

disease processes studied in a number of pairs of known monozygotic and dizygotic twins.

There is sound statistical evidence that these two types of twins do exist, but the methods commonly employed in distinguishing between these two types of twins are based upon a statistical consideration of their resemblances, and offer, unless adequately checked, an example of argument in a circle; a fault in logic peculiarly unfortunate seeing the manner of its employment.

The method proposed by Stocks is sufficiently definite for it to admit of a check being applied, and it is suggested that where only one of like-sexed twins are affected by a sex-linked character, such twins are dizygotic and constitute such a check.

Such a pair of twins is reported in detail; though they were not sufficiently alike to test Stocks' scheme severely, they had many features such as pigmentation, variation in growth and response to infection in which they closely resembled one another.

It is a pleasure to thank Dr. Elsie B. Wright for her kindness in calling my attention to this case of nystagmus which was admitted to the Babies' Hospital under her charge.

REFERENCES.

1. Galton, F., *J. Anthrop. Inst.*, London, 1876, V, 324 & 391.
2. Cockayne, E. A., *Brit. J. Child. Dis.*, London, 1911, VIII, 487.
3. Murray, G. R., *Lancet*, London, 1925, i, 529.
4. Glatzel, H., *Ztscher. f. klin. Med.*, Berlin, 1931, CXVI, 632.
5. Stransky, E., *Monatschr. f. Kinderh.*, Berlin, 1930, XLVIII, 406.
6. Curtius, F., & Korkhaus, G., *Ztschr. f. Konstitut.*, Berlin, 1930, XV, 229.
7. Siemens, H. W., *Die Zwillingspathologie*, Berlin, 1924.
8. v. Verschuer, O., *Ergebn. d. Inn. Med. u. Kinderh.*, Berlin, 1927, XXXI, 35.
9. Francioni, C., *Riv. di. clin. pediat.*, Firenze, 1919, XVII, 57.
10. Apert, E., *Les Jumeaux, Etude biologique, physiologique et medicale*, Paris, 1923.
11. Pommert, X., *Thése de Paris*, 1930.
12. Siemens, H. W.. *Arch. f. Dermat. u. Syph.*, Berlin, 1924, CXLVII, 210.
13. Korkhaus, G., *Viertelj. schr. f. Zahnheilk*, Berlin, 1929, XLV, 414.
14. Siemens, H. W., & Hunold, *Arch. f. Dermat. u. Syph.*, Berlin, 1924, CXLVII, 409.
15. Diehl, K., & v. Verschuer, O., *Beitr. z. Klin. d. Tuberk.*, Berlin, 1930, LXXV, 206.
16. Lange, J., *Allg. Ztschr. f. Psychiat.*, Berlin, 1929, XCIX, 122.
16. Lange, J., *Verbrechen als Schicksal*, Leipzig, 1929.
17. Bernheim-Karrer, J., *Ztschr. f. Kinderh.*, Berlin, 1929, XLVII, 427.
18. Newman, H. H., *Biology of Twins*, Chicago, 1917.
19. Weinberg, W., *Ztschr. f. Geburtsh. u. Gynak., Stuttgart*, 1902, XLVIII, 94.
20. Bonnevie, K., & Sverdrup, A., *J. Genetics*, London, 1926, XVI, 125.
21. Arey, L. B., *Anat. Rec., Philad.*, 1922, XXIII, 245.
22. Greulich, W. W., *Am. Naturalist*, N.Y., 1930, LXIV, 142.
23. Zeleny, C., *Science*, N.Y., 1921, LIII, 262.
24. Davenport, C. B., *Am. Naturalist*, N.Y., 1920, LIV, 122.
25. Curtius, F., *Arch. f. Gynäk.*, Berlin, 1930, CXL, 361.
26. v. Verschuer, O., *Munchen Med. Wchnschr.*, Munich, 1925, LXXII, 184.